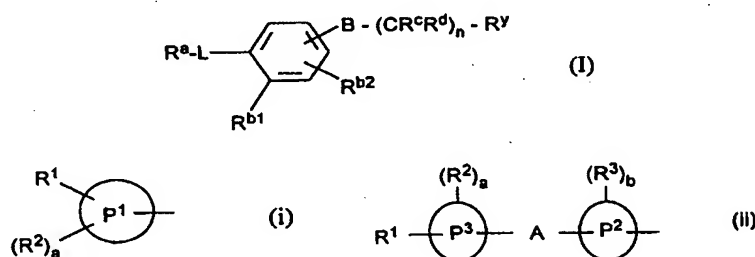




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(54) Title: ACETAMIDE AND UREA DERIVATIVES; PROCESS FOR THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF CNS DISORDERS



(57) Abstract

Compounds of formula (I), processes for their preparation and their use as CNS agents are disclosed, in which R^a is a group of formula (i), in which P^1 is phenyl, bicyclic aryl, a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur; or R^a is a group of formula (ii); L is a group of formula $-Y-C(=V)-DG-$, in which Y is $-NH-$, NR^5 where R^5 is C_{1-6} alkyl, or Y is $-CH_2-$ or $-O-$; V is oxygen or sulphur; D is nitrogen, carbon or a CH group, G is hydrogen or C_{1-6} alkyl providing that D is nitrogen or a CH group, or G together with R^{b1} forms a group W where W is $(CR^{16}R^{17})_t$ where t is 2, 3 or 4 and R^{16} and R^{17} are independently hydrogen or C_{1-6} alkyl or W is $(CR^{16}R^{17})_u-J$ where u is 0, 1, 2 or 3 and J is oxygen, sulphur, $CR^{16}=CR^{17}$, $CR^{16}=N$, $=CR^{16}O$, $=CR^{16}S$ or $=CR^{16}-NR^{17}$; B is CH_2 , oxygen, $S(O)_p$ where p is 0, 1 or 2, NR^6 where R^6 is hydrogen or C_{1-6} alkyl or B is $CR^7=CR^8$ where R^7 and R^8 are independently hydrogen or C_{1-6} alkyl; R^c and R^d are independently hydrogen or C_{1-6} alkyl; R^y is a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or R^y is a group of formula $-NR^eR^f$ in which R^e and R^f are independently hydrogen, C_{1-6} alkyl or aralkyl; R^{b1} and R^{b2} are independently hydrogen, halogen, hydroxy, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy or aryl, or R^{b1} together with G forms a group W as defined above; and n is 0, 1, 2, 3 or 4.

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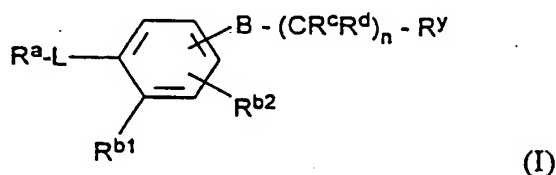
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ACETAMIDE AND UREA DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF CNS DISORDERS

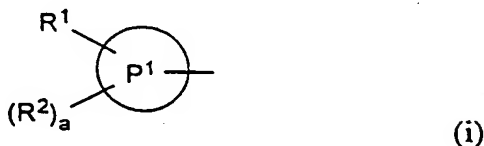
The present invention relates to novel aryl compounds processes for their preparation, and pharmaceutical compositions containing them.

WO 95/15954, WO 95/17398, WO 95/26328 and WO 96/06079 disclose a series of biphenyl amide derivatives which are said to possess 5HT_{1D} receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders such as depression. EPA 0533266/7/8 disclose a series of benzanilide derivatives which are said to possess 5-HT_{1D} receptor antagonist activity.

A structurally distinct class of compounds have now been found to exhibit combined 5HT_{1A}, 5HT_{1B} and 5HT_{1D} receptor antagonist activity. It is expected that such compounds will be useful for the treatment and prophylaxis of various CNS disorders with the advantage of a relatively fast onset of action. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



in which R^a is a group of formula (i)



in which P¹ is phenyl, bicyclic aryl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;

R¹ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, C₁₋₆alkanoyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_cCO₂R¹¹, (CH₂)_cNR¹⁰R¹¹,

$(CH_2)_cCONR^{10}R^{11}$, $(CH_2)_cNR^{10}COR^{11}$, $(CH_2)_cCO_2C_{1-6}alkyl$, $CO_2(CH_2)_cOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where R^9 , R^{10} and R^{11} are independently hydrogen or $C_{1-6}alkyl$ and c is 1 to 4;

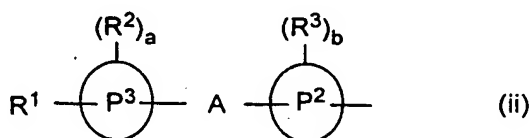
R^2 is hydrogen, halogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$,

- 5 $C_{3-6}cycloalkenyl$, $C_{1-6}alkoxy$, $C_{1-6}alkanoyl$, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10} , $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1 ;

a is 1, 2 or 3;

or R^a is a group of formula (ii)

10



wherein P^2 and P^3 are independently phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

15

A is a bond or oxygen, $S(O)_m$ where m is 0 to 2, carbonyl, or CH_2 or NR^4 where R^4 is hydrogen or $C_{1-6}alkyl$;

R^1 is as defined above for formula (i) or R^1 is a 5 to 7-membered heterocyclic ring, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by $C_{1-6}alkyl$, halogen or $C_{1-6}alkanoyl$;

20

R^2 and R^3 are independently hydrogen, halogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}cycloalkenyl$, $C_{1-6}alkoxy$, $C_{1-6}alkanoyl$, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10} , $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1 ;

25

and a and b are independently 1, 2 or 3;

L is a group of formula

- $Y - C(=V) - DG -$

30

in which Y is - $NH -$, NR^5 where R^5 is $C_{1-6}alkyl$, or Y is - $CH_2 -$ or - $O -$;

V is oxygen or sulphur;

- D is nitrogen, carbon or a CH group, G is hydrogen or C₁₋₆alkyl providing that D is nitrogen or a CH group, or G together with R^{b1} forms a group W where W is (CR¹⁶R¹⁷)_t where t is 2, 3 or 4 and R¹⁶ and R¹⁷ are independently hydrogen or C₁₋₆alkyl or W is (CR¹⁶R¹⁷)_u-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur,
- 5 CR¹⁶=CR¹⁷, CR¹⁶=N, =CR¹⁶O, =CR¹⁶S or =CR¹⁶-NR¹⁷;
- B is CH₂, oxygen, S(O)_p where p is 0, 1 or 2, NR⁶ where R⁶ is hydrogen or C₁₋₆alkyl or B is CR⁷=CR⁸ where R⁷ and R⁸ are independently hydrogen or C₁₋₆alkyl;
- R^c and R^d are independently hydrogen or C₁₋₆alkyl;
- 10 RY is a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or RY is a group of formula -NR^eR^f in which
- R^e and R^f are independently hydrogen, C₁₋₆alkyl or aralkyl;
- R^{b1} and R^{b2} are independently hydrogen, halogen, hydroxy, C₁₋₆alkyl, trifluoromethyl, C₁₋₆alkoxy or aryl, or R^{b1} together with G forms a group W as defined
- 15 above; and n is 0, 1, 2, 3 or 4.

C₁₋₆alkyl groups whether alone or as part of another group may be straight chain or branched. The term 'acyloxy' is used herein to describe a group -OC(O)C₁₋₆alkyl. The term 'aryl' is used herein to describe, unless otherwise stated, a group such as phenyl. The

20 term 'aralkyl' is used herein to describe, unless otherwise stated, a group such as benzyl.

The bicyclic aryl group represented by P¹, P² and/or P³, which may be partially saturated, is preferably naphthyl.

Examples of bicyclic heterocyclic rings containing 1 to 3 heteroatoms selected

25 from oxygen, nitrogen and sulphur include quinoline, isoquinoline, indole, benzofuran and benzothiophene rings. The heterocyclic groups can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

Examples of 5 to 7 membered heterocyclic rings containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur represented by P¹, P² and/or P³, include

30 thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl and pyrazinyl, preferably pyridyl.

R^1 is preferably a halogen atom for example, fluorine, chlorine or bromine, and R^2 and/or R^3 are each preferably hydrogen, halogen for example a chloro group or a C_{1-6} alkyl group for example a methyl group.

a and b are each preferably 1 or 2.

5 A is preferably a bond or oxygen, most preferably a bond.

In the group L, as defined above:-

Y is preferably -NH-.

V is preferably oxygen.

10 D is preferably nitrogen and G is preferably a hydrogen atom or together with R^{b1} forms group W, preferably $-(CH_2)_2$.

The groups R^{b1} and R^{b2} are preferably hydrogen or a halogen atom for example iodine, or R^{b1} together with G forms group W referred to above.

B is preferably CH_2 or oxygen, most preferably oxygen.

R^c and R^d are preferably hydrogen.

15 When RY is a 5- to 7-membered heterocyclic ring such groups can be linked to the rest of the molecule by a carbon atom or, when present, a suitable nitrogen atom.

Suitable examples of 5- to 7-membered heterocyclic rings include pyrrolidine, piperidine, piperazine, morpholine, optionally substituted by C_{1-6} alkyl, such as methyl. RY is preferably a piperidinyl group or a dialkylamino (e.g. dimethylamino) group.

20 n is preferably 2.

Preferably the group $B-(CR^cR^d)_n-RY$ has a meta relationship with respect to the group R^{aL} . Preferably the group R^{b2} has a para relationship with respect to the group R^{aL} .

25 Particularly preferred compounds according to the invention include:-

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]urea,

N-[4-bromo-3-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]naphth-1-ylacetamide,

30 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromophenyl carbamate,

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[(2-trifluoromethyl)phenyl]urea,

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[(4-fluoro-3-nitro)phenyl]urea,

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[4-phenoxyphenyl]urea,

- N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromophenylacetamide,
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea,
N-[2,3-dichlorophenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[naphth-1-yl]urea, N-[3-(2-
5 dimethylaminoethoxy)-4-iodophenyl]-N'-[2-nitrophenyl]urea, N-[3-chloro-4-
methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea, N-[3-(2-
dimethylaminoethoxy)-4-iodophenyl]-N'-[3-methylthiophenyl]urea,
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[4-methylthiophenyl]urea, N-[3-chloro-
2-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
10 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[3-methyl-4-(pyridin-4-
yl)phenyl]urea, N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2-fluoro-5-
nitrophenyl]urea, N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[phenyl]urea,
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2,3-dimethylphenyl]urea, N-[3-(2-
dimethylaminoethoxy)-4-iodophenyl]-N'-[3-ethylphenyl]urea,
15 N-[3-n-butoxyphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
N-[2,5-dichlorophenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
N-[4-chloro-2-trifluoromethylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromonaphth-1-ylacetamide,
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromo-3-methylphenylacetamide,
20 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
N-[4-n-butyl-3-(dimethylaminoethoxy)phenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
N-[4-n-butyl-3-(2-dimethylaminoethoxy)phenyl]-2,3-dichlorophenylacetamide,
N-[2,3-dichlorophenyl]-N'-[3-(3-dimethylaminopropyl)-4-iodophenyl]urea,
N-[3-(3-dimethylaminopropyl)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea,
25 N-[3-(3-dimethylaminopropyl)-4-iodophenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
N-[3-(3-Dimethylaminopropoxy)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea,
N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[5-(pyridin-4-yl)naphth-1-yl]urea,
N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-5-(pyridin-4-yl)naphth-1-ylacetamide,
N-[4-Methoxy-5-((S)-1-methyl-2-pyrrolidinylmethoxy)phenyl]-4-(pyridin-4-yl)naphth-1-
30 ylacetamide,
1-(2,3-Dichlorophenylaminocarbonyl)-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-iodo-
1H-indole,

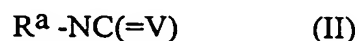
- 2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1-[4-(pyridin-4-yl)naphth-1-ylamino-carbonyl]-1H-indole,
- 5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
- 5 5-Bromo-2,3-dihydro-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-6-(2-dimethylaminoethoxy)-1H-indole,
- 5-Chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
- 5-Chloro-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-
- 10 dimethylaminoethoxy)-1H-indole,
- 2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1-(4-(pyridin-4-yl)naphth-1-ylaminocarbonyl)-1H-indole,
- 1-[3-Chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole,
- 15 2,3-Dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole,
- 5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole,
- 2,3-Dihydro-6-(2-imethylaminoethoxy)-5-ethyl-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-
- 20 indole,
- N-[4-Bromo-3-(2-dimethylaminoethoxy)phenyl]-2,3-dihydro-4-(pyridin-4-yl)naphth-1-ylacetamide,
- N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-iodo-3-(1-methylpiperidin-4-yloxy)phenyl]urea,
- 25 N-[4-Chloro-3-(1-methyl-4-piperidinyloxy)phenyl]-N'-[3-chloro-4-(pyridin-4-yl)phenyl]urea,
- 5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(1-methylpiperidin-4-yloxy)-1H-indole,
- N-[4-Chloro-3-(1-methylpiperidin-4-yloxy)phenyl]-N'-[4-(pyridin-4-yl)-3-
- 30 trifluoromethylphenyl]urea,
- N-[4-Chloro-3-(2-dimethylaminoethoxy)phenyl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]urea,

- 5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole,
5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole,
5 5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)oxy]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-3-yl)oxy]-1H-indole,
5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole,
10 5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[5-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
N-[4-Acetylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
N-[3-Acetylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
15 2,3-Dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
5-Bromo-2,3-dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
5-Chloro-2,3-dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
20 2,3-Dihydro-6-(3-dimethylaminopropyl)-5-iodo-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
N-[2,3-Dichloro-4-(pyridin-4-yl)phenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
25 5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
5-Bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole
or pharmaceutically acceptable salts thereof.
- 30 Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

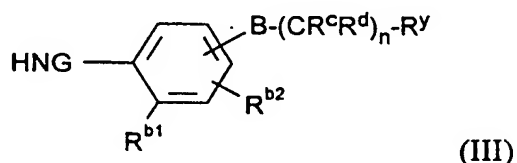
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates.

Compounds of the invention can be prepared using procedures known in the art.

- 5 In a further aspect the present invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises:
(a) where D is nitrogen and Y is NH, coupling a compound of formula (II):

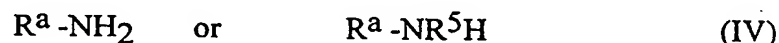


- 10 in which R^a and V are as defined in formula (I) or a protected derivative thereof with a compound of formula (III).



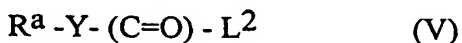
- 15 in which R^{b1} , R^{b2} , R^c , R^d , R^Y , B, G and n are as defined in formula (I), or a protected derivative thereof; or

(b) where D is nitrogen and Y is NH or NR^5 , reacting a compound of formula (IV)



- 20 in which R^a and R^5 are as defined in formula (I) with a compound of formula (III) together with an appropriate urea forming agent;

(c) where D is nitrogen, reacting a compound of formula (V)



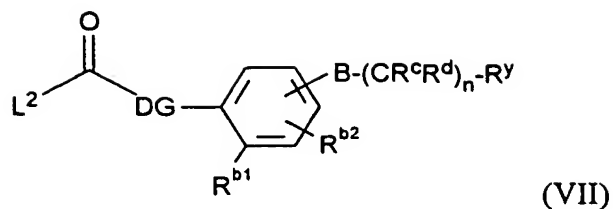
in which R^a is as defined in formula (I),

- 25 Y is $-CH_2-$ or $-O-$ and L^2 is an appropriate leaving group, with a compound of formula (III)

(d) where D is carbon or CH, reacting a compound of formula (VI)



in which R^a is as defined in formula (I) with a compound of formula (VII)



in which D is carbon or CH, R^{b1} , R^{b2} , R^c , R^d , R^y , B, G and n are as defined in formula (I) and L^2 is an appropriate leaving atom and optionally thereafter:

- 5
 - removing any protecting groups,
 - converting a compound of formula (I) into another compound of formula (I),
 - forming a pharmaceutically acceptable salt.

10 The reaction in process (a) is conveniently effected in an organic solvent such as dichloromethane.

In process (b) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

15 In process (c) the leaving group L^2 may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

20 In process (d) the leaving group L^2 may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques.

25 Intermediate compounds of formula (II), (III), (IV), (V), (VI) and (VII) can be prepared using standard procedures known in the art.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected

as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

5HT_{1A/1B/1D} receptor antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa ;and sleep disorders. Other CNS disorders include motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

5HT_{1A/1B/1D} receptor antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

5 The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

15 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

25 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is 30 suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene

oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

5 The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number
10 of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Description 1

2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-isocyanate

15 A stirred suspension of 2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (3.0g, 0.010 mole, EP 0533268A1) in dichloromethane (80ml) was treated with oxalyl chloride (1.3ml, 0.015 mole) and DMF (1 drop), then stirred at room temp for 4h. The resulting solution was concentrated *in vacuo* to afford the acid chloride as a yellow solid. This was dissolved in dichloromethane (100ml) and cooled to 0°C. To
20 this was added tetrabutylammonium iodide (50mg) followed by a solution of sodium azide (0.91g, 0.014 mole) in water (20ml) and the mixture stirred vigorously for 3h. The mixture was then diluted with water (75ml) and the dichloromethane layer separated, dried (Na₂SO₄) and concentrated *in vacuo* but not to dryness. The residue was dissolved in toluene (150ml) and heated under reflux with stirring for 1.5h. The toluene was
25 removed *in vacuo* to afford the title compound as a pale orange solid (3.15g, 100%).
¹H NMR (250MHz, CDCl₃) δ (ppm): 7.90 (s, 1H), 7.85 (dd, 1H), 7.25 (d, 2H and d, 1H), 7.10 (d, 2H), 2.61 (s, 3H), 2.26 (s, 3H).

Description 2

30 4-Bromo-3-methylphenyl isocyanate

The title compound was prepared from 4-bromo-3-methylbenzoic acid using a similar procedure to Description 1.

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.54 (d, 1H), 7.06 (d, 1H), 6.88 (dd, 1H), 2.46 (s, 3H).

Description 3

5 4-(Pyridin-4-yl)naphthyl-1-amine

A stirred suspension of 4-bromonaphth-1-ylamine (10g, 45 mmole) in 1,2-dimethoxyethane (400ml) and water (100ml) containing sodium carbonate (14g) was flushed with argon for 0.3h. Tetrakis(triphenylphosphine)palladium (0) (2.75g, 2.4 mmole) was added followed by 4-pyridylboronic acid (5.7g, 46 mmole) and the mixture
10 heated at reflux for 5h. The mixture was concentrated *in vacuo* to a brown slurry and partitioned between dichloromethane and water. The aqueous was further extracted with dichloromethane and the combined organics dried (Na₂SO₄) and concentrated *in vacuo* to a brown solid (13.2g). Purification of the solid by flash chromatography eluting with ethyl acetate afforded the title compound as a yellow crystalline solid (7.8g, 78%).

15 ¹H NMR (250MHz, CDCl₃) δ (ppm): 8.68 (d, 2H), 7.90 (d, 2H), 7.30 (m, 5H), 6.84 (d, 1H), 4.32 (s, 2H).

Description 4

3-Methyl-4-(pyridin-4-yl)benzoic acid

20 A stirred mixture of 4-bromo-3-methylbenzoic acid (3.5g, 0.016 mole), 4-pyridylboronic acid (2.0g, 0.016 mole) and sodium carbonate (5.1g, 0.048 mole) in water (100ml) and DME (100ml) was de-gassed by bubbling argon through for 15 minutes, then tetrakis (triphenylphosphine) palladium (0) (300mg) was added and the mixture was heated at reflux under argon for 18h. The mixture was then cooled, concentrated to approx 100ml
25 volume *in vacuo* and acidified to pH 5 by addition of 2M HCl acid. The precipitate was filtered off, washed with water and dried to afford the title compound as a beige solid (3.13g, 92%).

¹H NMR (250MHz, d⁶DMSO) δ (ppm): 8.66 (d, 2H), 7.90 (d, 1H), 7.85 (dd, 1H), 7.42 (d, 2H), 7.36 (d, 1H), 2.29 (s, 3H).

30

Description 5

3-Methyl-4-(pyridin-4-yl)phenyl isocyanate

The title compound was prepared from 3-methyl-4-(4-pyridyl)benzoic acid (D4) using a similar procedure to Description 1.

^1H NMR (250MHz, d^6DMSO) δ (ppm): 9.72 (d, 2H), 7.70 (dd, 1H), 7.52 (d, 2H), 7.52 (d, 1H), 7.31 (d, 1H), 2.38 (s, 3H).

5

Description 6

4-Bromo-3-methylbenzyl alcohol

A stirred suspension of 4-bromo-3-methylbenzoic acid (25g, 0.12 mole) in THF (250 ml) was treated with LiAlH_4 (9.11g, 0.24 mole) in THF (200 ml) and heated under reflux for 10 4h. The reaction mixture was treated with 1M NaOH and concentrated *in vacuo*. Ether was then added and the mixture filtered. The filtrate was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation to afford the title compound (8.5g, 35%).

^1H NMR (250 MHz CDCl_3) δ (ppm) : 7.52 (d, 1H), 7.2 (s, 1H), 7.01 (d, 1H), 4.52 (s, 2H), 15 3.5-3.45 (s, 1H), 2.45 (s, 3H).

Description 7

4-Bromo-3-methylphenylacetonitrile

A stirred suspension of 4-bromo-3-methylbenzyl alcohol (D6, 7.5g, 0.037 mole) in 20 dichloromethane (300 ml) was treated with triethylamine (5.2ml) and methanesulphonyl chloride (3.03ml, 0.039mole), whilst maintaining a temperature below 20°C and stirred overnight. The reaction mixture was washed with saturated NaHCO_3 solution (150ml), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was suspended in methanol (500ml) and treated with sodium cyanide (2.14g, 0.044 mole) and heated under reflux for 25 3.5h. The reaction mixture was partitioned between aqueous K_2CO_3 solution and dichloromethane and the organic layer separated, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by distillation (2.81g, 37%).

^1H NMR (250 MHz, CDCl_3) δ (ppm) : 7.59-7.48 (m, 1H), 7.3-7.12 (m, 1H), 7.11-6.96 (m, 1H), 3.7 (s, 3H), 2.44 (s, 3H).

30

Description 8

4-Bromo-3-methylphenylacetic acid

A stirred suspension of 4-bromo-3-methylphenylacetonitrile (D7, 2.5g, 11.8 mmole) in 5M HCl/water (150 ml) was heated under reflux for 14 days. The reaction mixture was then concentrated *in vacuo*, basified with aqueous K₂CO₃ and shaken with ether. The aqueous phase was acidified with 5M HCl and extracted with ether. The organic extract
5 was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound (2g, 74%).
¹H NMR (250 MHz, CDCl₃) δ(ppm) : 7.35 (d, 1H), 7.02 (d, 1H), 6.85 (d, 1H), 3.45 (s, 2H), 2.25 (s, 3H).

Description 9

10 4-(Pyridin-4-yl)naphth-1-ylacetic acid

4-Bromonaphth-1-ylacetic acid (1g, 3.78 mmole, J. Org. Chem., 1951, 16, 1588) in 1,2-dimethoxyethane (50ml) was treated with 4-pyridylboronic acid (465mg, 3.78 mmole), sodium hydrogen carbonate (952mg, 11.3 mmole) and water (10ml). A stream of argon was bubbled through the mixture for 15 min, then tetrakis (triphenylphosphine) palladium
15 (0) (200mg 0.17 mmole) was added and the mixture heated under reflux for 18h. The mixture was then concentrated *in vacuo* to a gum, which was partitioned between 2N sodium hydroxide solution and dichloromethane. The aqueous layer was separated, adjusted to pH 0 with 6N hydrochloric acid and washed with dichloromethane; then adjusted to pH 7 by addition of aqueous potassium carbonate solution and extracted with
20 dichloromethane. The dichloromethane extract was dried (Na₂SO₄) and concentrated *in vacuo* to give the title compound, which crystallised from ether as needles mp 210-215°C (465mg, 46%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.55 (d, 2H), 8.0 (d, 1H), 7.7 (d, 1H), 7.5 - 7.3 (m, 5H), 7.2 (d, 1H), 6.1 (br s, 1H), 4.0 (s, 2H).

25

Description 10

(3-Acetamidophenyl) butyrate

3-Acetamidophenol (50g, 0.33 mole) in dichloromethane (250 ml) was treated with butyryl chloride (32.67g, 0.33 mole), and pyridine (26.07g, 0.33 mole) was added at such
30 a rate that the temperature did not rise above 30°C. After standing at room temperature overnight, the reaction was washed with 5N HCl and saturated aqueous potassium carbonate solution. The reaction was concentrated *in vacuo* to a gum which was

crystallised from ether/petrol to give the title compound as cubes mp 76 - 79°C (65.84g, 90%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.05 (s, 1H), 7.45 (s, 1H), 7.2 (t, 1H), 7.1 (d, 1H), 6.75 (d, 1H), 2.5 (t, 2H), 2.05 (s, 3H), 1.75 (sextet, 2H), 1.05 (t, 3H).

5

Description 11

4-Butyryl-3-hydroxyacetanilide

(3-Acetamidophenyl) butyrate (D10, 26.2g, 0.118 mole) was intimately mixed with aluminium trichloride powder (39g, 0.295 mole) and plunged into an oil bath at 175°C under argon, when a vigorous frothing and evolution of hydrogen chloride gas occurred. The resulting foam was allowed to cool and broken up to a powder. The powder was reheated at 175°C on an oil bath for 2.5h. The reaction was then added to a mixture of ice in 2N sulphuric acid, which was stirred overnight. The resulting slurry was filtered to give the title compound as a cream powder (21.5g, 82%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 12.65 (s, 1H), 7.75 (s, 1H), 7.7 (d, 1H), 7.2 (dd, 1H), 7.07 (d, 1H), 2.9 (t, 2H), 2.2 (s, 3H), 1.75 (sextet, 2H), 1.05 (t, 3H).

Description 12

4-Butyl-3-hydroxyacetanilide

4-Butyryl-3-hydroxyacetanilide (D11, 16g, 72 mmole) in acetic acid (150ml) was treated with 10% palladium on carbon (3g) under an atmosphere of hydrogen at 3.5 bar and 50°C for 48h. The reaction was then filtered through kieselguhr and concentrated *in vacuo* to a gum. The gum was chromatographed on silica in a gradient of 10-40% ethyl acetate/dichloromethane. The main fraction eluted in 30% ethyl acetate/dichloromethane to give the title compound, which crystallised from ether/petrol as needles m.p. 139-140°C (2.65g, 18%).

¹H NMR (250MHz, d⁶DMSO) δ (ppm): 9.7 (s, 1H), 9.2 (s, 1H), 7.25 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 2.45 (t, 2H), 2.0 (s, 3H), 1.5 (quintet, 2H), 1.3 (sextet, 2H), 0.9 (t, 3H).

Description 13

4-Butyl-3-(2-dimethylaminoethoxy)acetanilide

4-Butyl-3-hydroxyacetanilide (D12, 1g, 4.8 mmole) in 1,2-dimethoxyethane (20ml) was treated with 2-dimethylaminoethyl chloride hydrochloride (1.38g, 9.6 mmole), potassium

carbonate (1.65g, 12 mmole) and water (5ml), and the reaction heated at reflux under argon for 4h. Further portions of 2-dimethylaminoethyl chloride hydrochloride (1.38 g, 9.6 mmole) and potassium carbonate (1.65 g, 12 mmole) were added and the reaction heated under reflux for a further 2 days. The reaction was then concentrated *in vacuo* to a gum and partitioned between 5N HCl and dichloromethane. The aqueous solution was separated and basified with 2N sodium hydroxide solution. The product was recovered by extraction into dichloromethane, the organic layer separated, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a gum (1.2g, 89%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.5 (s, 1H), 7.25 (s, 1H), 7.05 (d, 1H), 6.82 (d, 1H), 4.05 (t, 2H), 2.75 (t, 2H), 2.55 (t, 2H), 2.35 (s, 6H), 2.15 (s, 3H), 1.53 (quintet, 2H), 1.35 (sextet, 2H), 0.9 (t, 3H).

Description 14

4-Butyl-3-(2-dimethylaminoethoxy)aniline

4 Butyl-3-(2-dimethylaminoethoxy)acetanilide (D13, 1.1g, 3.95 mmole) in ethanol (25ml) was treated with 2N sodium hydroxide (25 ml) and heated under reflux for a period of 18h. The reaction was then concentrated *in vacuo* to remove the ethanol and the product recovered by extraction into dichloromethane. The organic layer was separated, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a gum (0.85g, 77%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 6.8 (d, 1H), 6.1 (m, 2H), 3.95 (t, 2H), 3.5 (br s, 2H), 2.7 (t, 2H), 2.4 (t, 2H), 2.25 (s, 6H), 1.45 (quintet, 2H), 1.3 (sextet, 2H), 0.85 (t, 3H).

Description 15

2,3-Dichlorophenylacetonitrile

A stirred suspension of 2,3-dichlorobenzyl chloride (20g, 0.10 mole) in ethanol/water (95:5) (150ml) was treated with sodium cyanide (6g, 0.12 mole) in water (25ml), heated under reflux for 8h and then left to stand overnight. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane and aqueous K₂CO₃ solution. The organic layer was dried (Na₂SO₄), concentrated *in vacuo*, washed with petrol ether and concentrated *in vacuo* to afford the title compound (14.59g, 77%).

¹H NMR (250 MHz CDCl₃) δ(ppm) : 7.56-7.39 (m, 2H), 7.32-7.15 (m, 1H), 3.91 (s, 2H).

Description 16

Ethyl 2,3-dichlorophenylacetate

A stirred suspension of 2,3-dichlorophenylacetonitrile (D15, 14g, 75 mmole) in ethanol (200ml) was treated with conc sulphuric acid (20ml) and heated under reflux for 3 days.

The reaction mixture was then concentrated *in vacuo* and partitioned between
5 dichloromethane and water. The organic layer was separated, dried (Na₂SO₄), and concentrated *in vacuo* to afford the title compound (16.45g, 94%).

¹H NMR (250 MHz, CDCl₃) δ(ppm) : 7.4 - 7.3 (m, 1H), 7.2 - 7.15 (m, 2H), 4.20 - 4.18 (q, 2H), 3.75 (s, 2H), 1.27 - 1.15 (t, 3H)

10 Description 17**2,3-Dichlorophenylacetic acid**

A stirred suspension of ethyl 2,3-dichlorophenylacetate (D16, 4.4g, 19 mmole) in 5M HCl/water (300 ml) was heated under reflux overnight. The reaction mixture was concentrated *in vacuo* to afford the title compound (2.5g, 65%).

15 ¹H NMR (250 MHz, CDCl₃) δ(ppm) 7.45 - 7.36 (m, 1H), 7.23 - 7.12 (m, 2H), 3.85 (s, 2H).

Description 18**3-(3-Aminophenyl)-N,N-dimethylprop-2-enamide**

20 A stirred solution of 3-bromoaniline (6.3ml, 0.058mole) and N,N-dimethylacrylamide (6.6ml, 0.064mole) in dry DMF (28ml) was treated with triethylamine (20ml, 0.14mole), then de-gassed by bubbling argon through for 15 min. Palladium (II) acetate (260mg, 0.0012 mole) and tri (σ-tolyl)phosphine (1.4g, 0.0046 mole) were added and the mixture heated at 100 - 110°C for 1.5h, then allowed to cool and concentrated *in vacuo* to approx
25 20ml volume. The residue was treated with water (200ml) and ethyl acetate (250ml), shaken well and then filtered through a plug of kieselguhr. The organic layer was separated, washed with water (2x200ml), dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow oil, which was crystallised from ethyl acetate/ether to afford the title compound as a yellow solid (5.4g, 49%).

30 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.69 (d, 1H), 7.30 - 7.20 (m, 1H), 7.02 (d, 1H), 7.00 - 6.88 (m, 2H), 6.77 (dd, 1H), 3.85 (br s, 2H), 3.24 (s, 3H), 3.16 (s, 3H).

Description 19

3-(3-Aminophenyl)-N,N-dimethylpropionamide

A stirred solution of 3-(3-aminophenyl)-N,N-dimethylprop-2-enamide (D18, 4.5g, 0.024 mole) in ethanol (150ml) was hydrogenated over 5% Pd-C (1.0g) at atmospheric temperature and pressure for 90h. The catalyst was removed by filtration through
5 kieselguhr and the filtrate concentrated *in vacuo* to afford the title compound as a pale brown oil (4.5g, 100%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.14 - 7.04 (m, 1H), 6.67 - 6.48 (m, 3H), 3.62 (br s, 2H), 2.96 (s, 3H), 2.94 (s, 3H), 2.87 (t, 2H), 2.59 (t, 2H).

10 Description 20**3-(5-Amino-2-iodophenyl)-N,N-dimethylpropionamide**

A stirred solution of 3-(3-aminophenyl)-N,N-dimethylpropionamide (D19, 2.68g, 0.014 mole) and anhydrous potassium carbonate (2.13g, 0.016mole) in a mixture of
15 dichloromethane (130ml) and methanol (50ml) at 0°C under argon was treated portionwise over 10 min with benzyltrimethylammonium dichloroiodate (4.87g, 0.014 mole). The mixture was kept at 0°C for 0.5h, then allowed to warm to room temperature over 1h, then concentrated *in vacuo* and the residue treated with dichloromethane (120ml) and 5% aqueous Na₂S₂O₅ solution (50ml) and shaken well. The organic layer was
20 separated, dried (Na₂SO₄) and concentrated *in vacuo* to leave the title compound as a brown oil (96%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.50 (d, 1H), 6.67 (d, 1H), 6.30 (dd, 1H), 3.50 (br s, 2H), 2.95 (s, 6H), 2.93 (t, 2H), 2.58 (t, 2H).

Description 21**25 3-(3-Dimethylaminopropyl)-4-iodoaniline**

A stirred solution of 3-(5-amino-2-iodophenyl)-N,N-dimethylpropanamide (D20, 5.0g, 0.016mole) in THF (70ml) under argon at 20°C was treated with 1M borane in THF (32ml, 0.032 mole) and then heated under reflux for 2h. Further borane-THF was added (32ml) and reflux continued for a further 2h. The reaction mixture was allowed to cool,
30 then treated cautiously with conc. HCl acid (15ml) in methanol (85ml). After 64 h, at room temp. the mixture was concentrated *in vacuo* and the residue basified by addition of 10% Na₂CO₃ solution and extracted with ethyl acetate. The organic extract was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was dissolved in ethanol (60ml),

- treated with cesium fluoride (1.3g) and anhydrous potassium carbonate (1.3g) and heated under reflux for 10 h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (100ml) and dichloromethane (100ml), shaken well and the organic layer separated, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a purple oil. This was converted to its hydrochloride salt, which precipitated from acetone as a beige solid.

^1H NMR (free base) (250 MHz, CDCl_3) δ (ppm): 7.52 (d, 1H), 6.60 (d, 1H), 6.28 (dd, 1H), 3.65 (br s, 2H), 2.63 (t, 2H), 2.33 (t, 2H), 2.25 (s, 6H), 1.83 - 1.65 (m, 2H).

10. **Description 22**

5-(Pyridin-4-yl)naphth-1-ylamine

The title compound was prepared from 5-bromonaphth-1-ylamine (JP 08151353A2) and 4-pyridineboronic acid using a similar procedure to Description 3 as a yellow solid (61%).

- 15 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 8.75 - 8.67 (m, 2H), 7.93 (d, 1H), 7.70 - 7.35 (m, 4H), 7.28 - 7.20 (m, 2H), 6.85 - 6.80 (m, 1H), 4.25 (s, 2H).

Description 23

3-Chloro-4-(pyridin-4-yl)aniline

- 20 3-Chloro-4-bromoacetanilide was reacted with 4-pyridineboronic acid using a similar procedure to Description 3 to afford 3-chloro-4-(4-pyridyl)acetanilide. This material was hydrolysed by heating under reflux in a mixture of 2M NaOH solution and ethanol for 6 h to afford the title compound as a pale yellow solid (5.5g, 73%).

- 25 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 8.65 - 8.58 (m, 2H), 7.38 - 7.33 (m, 2H), 7.13 (d, 1H), 6.80 (d, 1H), 6.64 (dd, 1H), 3.90 (brs, 2H).

Description 24

5-(Pyridin-4-yl)naphth-1-ylacetic acid

- 30 The title compound was prepared from 5-bromonaphth-1-ylacetic acid (Bull. Soc. Chim. Fr. 1968, 7, 2957) and 4-pyridylboronic acid using a similar procedure to Description 3.

^1H NMR (250MHz, CDCl_3) δ (ppm): 8.72 (d, 2H), 8.13 (d, 1H); 7.76 (d, 1H); 7.60 (t, 1H), 7.40 - 7.50 (m, 3H), 7.44 (d, 2H), 4.12 (s, 2H).

Description 25**3-(3-Dimethylaminopropoxy)-4-iodoacetanilide**

A stirred solution of 3-hydroxy-4-iodoacetanilide (2.5g, 0.0090 mole) in DME (60ml) was treated with 3-dimethylaminopropyl chloride hydrochloride (1.74g, 0.011 mole) and a solution of potassium carbonate (5g) in water (10ml), then heated at reflux under argon for 4h. The mixture was allowed to cool, concentrated *in vacuo* and the residue acidified with 1M HCl acid (150ml) and washed with ethyl acetate (150ml). The acid solution was then basified with solid K₂CO₃ and extracted with ethyl acetate. The extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a beige solid (3.0g, 92%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.62 (d, 1H), 7.47 (s, 1H), 7.36 (d, 1H), 6.67 (dd, 1H), 4.04 (t, 2H), 2.51 (t, 2H), 2.26 (s, 6H), 2.16 (s, 3H), 1.98 (quintet, 2H).

Description 26**3-(3-Dimethylaminopropoxy)-4-iodoaniline**

A stirred suspension of 3-(3-dimethylaminopropoxy)-4-iodoacetanilide (D25, 3.0g, 0.0083 mole) in 2M NaOH solution (80ml) and ethanol (50ml) was heated at reflux under argon for 6h, then allowed to cool, concentrated *in vacuo* to approx. 80ml volume and extracted with ethyl acetate. The organic solution was extracted with 1M HCl acid, and the acid solution basified by the addition of solid K₂CO₃ and extracted with ethyl acetate. The organic extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a beige solid (1.47g, 55%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.43 (d, 1H), 6.20 (d, 1H), 6.09 (dd, 1H), 3.99 (t, 2H), 3.71 (brs, 2H), 2.51 (t, 2H), 2.26 (s, 6H), 1.97 (quintet, 2H).

Description 27**1-Acetyl-6-amino-2,3-dihydro-1H-indole**

2,3-Dihydro-6-nitro-1H-indole (15.63g, 0.095 mol) was refluxed for 0.25h in acetic anhydride (100ml), cooled, and the precipitate filtered and washed with water, before drying *in vacuo*. This material (16.6g, 0.08 mol) was hydrogenated in ethanol (500ml) over 10% palladium on charcoal (3.4g of 50% paste in water). The catalyst was removed by filtration and the filtrate was evaporated to leave the title compound as an off-white/cream powder (12.59g, 89%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.66 (s, 1H), 6.92(d, 1H), 6.35 (d, 1H), 4.01 (t, 2H), 3.65 (br s, 2H), 3.05 (t, 2H), 2.2 (s, 3H).

Description 28

5 1-Acetyl-2,3-dihydro-6-hydroxy-1H-indole

A solution of 1-acetyl-6-amino-2,3-dihydro-1H-indole (D27, 12g, 0.068 mol) in concentrated sulfuric acid (9ml) and water (137 ml) was cooled to 0°C and diazotised by the dropwise addition of sodium nitrite (4.8g) in water (34 ml), maintaining the temperature at below 5°C. After 0.5h, the reaction mixture was added to a boiling stirred solution of copper (II) sulfate (69g) in water (120ml). After evolution of nitrogen had ceased, the mixture was cooled, and the precipitate collected by filtration, washed with water, then dried. The compound was purified by column chromatography of its O-acetyl derivative, then hydrolysed with aqueous NaOH at 20°C over 18 h to afford the title compound as a grey solid (2.6g, 22%).

15 ¹H NMR (250 MHz, d⁶DMSO) δ (ppm): 9.20 (s, 1H), 7.58 (d, 1H), 6.96 (d, 1H), 6.35 (dd, 1H), 4.04 (t, 2H), 2.98 (t, 2H), 2.12 (s, 3H).

Description 29

1-Acetyl-2,3-dihydro-6-hydroxy-5-iodo-1H-indole

20 A stirred suspension of powdered 1-acetyl-2,3-dihydro-6-hydroxy-1H-indole (D28, 2.8g, 0.016 mole) in a mixture of DCM (400ml) and methanol (170°C) at 0°C under argon was treated portionwise over 5 min with benzyltrimethylammonium dichloroiodate (6.05g, 0.017 mole), then kept at 0°C for 20 min and allowed to warm to room temperature over 1h. The fine precipitate was filtered off, washed with DCM and dried, to afford the title compound as a white solid (1.88g). Additional product was obtained as a pale brown solid on concentrating the filtrate to approx. 300ml volume and filtering off the solid (1.56g).

25 ¹H NMR (250 MHz, d⁶DMSO) δ (ppm): 10.18 (s, 1H), 7.77 (s, 1H), 7.43 (s, 1H), 4.05 (t, 2H), 3.00 (t, 2H), 2.13 (s, 3H).

30

Description 30

1-Acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1H-indole

The title compound was prepared from 1-acetyl-2,3-dihydro-6-hydroxy-5-iodo-1H-indole (D29) and 2-dimethylaminoethyl chloride hydrochloride using a similar procedure to Description 25 (70%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.90 (s, 1H), 7.51 (s, 1H), 4.14 (t, 2H), 4.07 (t, 2H),
5 3.12 (t, 2H), 2.81 (t, 2H), 2.38 (s, 6H), 2.21 (s, 3H).

Description 31

2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1H-indole

A stirred suspension of 1-acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1H-
10 indole (D30, 1.0g, 2.7 mmol) in a mixture of 2M NaOH solution (20ml) and ethanol (20ml) was de-gassed by bubbling argon through for 20 min, then heated under reflux for 6h. The mixture was allowed to cool, concentrated *in vacuo* to approx. 20ml volume, then extracted with DCM. The extract was dried (Na₂SO₄) and concentrated *in vacuo* to afford a brown oil (0.52g); which consisted of an approx. 2:1 mixture of title compound
15 to de-iodinated material. The mixture was re-iodinated using a similar procedure to Description 29 to afford the title compound as a dark brown oil.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.39 (s, 1H), 6.23 (s, 1H), 4.04 (t, 2H), 3.8 (br s, 1H), 3.57 (t, 2H), 2.96 (t, 2H), 2.79 (t, 2H), 2.37 (s, 6H).

20 Description 32

1-Acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole

The title compound was prepared from 1-acetyl-2,3-dihydro-6-hydroxy-1H-indole (D28) following a similar procedure to Description 25.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.91 (d, 1H), 7.03 (d, 1H), 6.60 (dd, 1H), 4.02 -
25 4.09 (m, 4H), 3.11 (t, 2H), 2.71 (t, 2H), 2.33 (s, 6H), 2.21 (s, 3H).

Description 33

1-Acetyl-5-bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole

To a stirred solution of 1-acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D32,
30 500mg, 2.0 mmol) in glacial acetic acid (20ml) was added N-bromosuccinimide (395mg, 2.2 mmol) portionwise over 3-5 min. After 3 h, water (30ml) was added and the mixture basified to pH10 with K₂CO₃ (s) and extracted with CH₂Cl₂ (3x50ml). The organics were

separated, combined, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a pale brown solid (596mg, 90%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.97 (s, 1H), 7.29 (s, 1H), 4.15 (t, 2H), 4.07 (t, 2H), 3.13 (t, 2H), 2.80 (t, 2H), 2.37 (s, 6H), 2.22 (s, 3H).

5

Description 34

5-Bromo-6-2,3-dihydro-(2-dimethylaminoethoxy)-1H-indole

A stirred solution of 1-acetyl-5-bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D33, 360mg, 1.1mmol) in 2M HCl (50ml) was heated under reflux for 2 h then cooled to room temperature, basified to pH10 with K₂CO₃ (s) and extracted into CH₂Cl₂ (3x50ml). The organics were combined, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a yellow/brown oil (242mg, 77%).

10

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.20 (s, 1H), 6.28 (s, 1H), 4.05 (t, 2H), 3.76 (br s, 1H), 3.57 (t, 2H), 2.96 (t, 2H), 2.77 (t, 2H), 2.36 (s, 6H).

15

Description 35

1-Acetyl-5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole

The title compound was prepared from 1-acetyl-6-(2-dimethylaminoethoxy)-1H-indole (D32) and N-chlorosuccinimide using a similar procedure to Description 33.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.99 (s, 1H), 7.14 (s, 1H), 4.20 (t, 2H), 4.08 (t, 2H), 3.13 (t, 2H), 2.87 (t, 2H), 2.43 (s, 6H), 2.22 (s, 3H).

20

Description 36

5-Chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole

The title compound was prepared from 1-acetyl-5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D35) using a similar procedure to Description 34.

25

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.05 (s, 1H), 6.29 (s, 1H), 4.06 (t, 2H), 3.75 (br s, 1H), 3.57 (t, 2H), 2.96 (t, 2H), 2.77 (t, 2H), 2.36 (s, 6H).

30

Description 37

1-Acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-vinyl-1H-indole

To a stirred solution of 1-acetyl-5-bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D33, 1.0g, 3.1 mmol) in dry DMF (25ml) was added vinyltributyltin (1.34ml, 4.6

mmole). The mixture was degassed for 20 min using argon, then NEt₃ (0.618g, 6.1 mmole) was added and the mixture gently degassed for 3 min. Tetrakis (triphenylphosphine) palladium (0) (0.260g) was added, a condenser attached and the mixture was heated at 100°C under argon for 10 h, then cooled. The DMF was removed
5 *in vacuo* and the residue partitioned between ethyl acetate (50ml) and 2M HCl (aq) (140ml). The ethyl acetate layer was washed with 2M HCl (2x50ml), then the aqueous extracts were combined, basified to pH10 with K₂CO₃(s) and extracted with CH₂Cl₂ (3x100ml). The organics were combined, dried (Na₂SO₄) and concentrated *in vacuo* to afford a yellow solid, which was purified by column chromatography on basic alumina
10 eluting with 1:1 EtOAc:CH₂Cl₂. The title compound was obtained as a pale yellow solid (0.340g, 41%)

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.90 (s, 1H), 7.29 (s, 1H), 7.04 (dd, 1H), 5.53 (dd, 1H), 5.14 (dd, 1H), 4.14 (t, 2H), 4.06 (t, 2H), 3.14 (t, 2H), 2.76 (t, 2H), 2.44 (s, 6H), 2.23 (s, 3H).

15

Description 38

1-Acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole

A solution of 1-acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-vinyl-1H-indole (D37, 329mg, 1.2 mmol) in ethanol (50ml) was hydrogenated over 10% Pd/C catalyst at room
20 temperature and pressure. After 40 h the catalyst was filtered off and the filtrate concentrated *in vacuo* to yield the title compound as a pale yellow solid (331mg, 100%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.87 (s, 1H), 6.98 (s, 1H), 4.49 (t, 2H), 4.07 (t, 2H), 3.48 (t, 2H), 3.14 (t, 2H), 2.92 (s, 6H), 2.56 (q, 2H), 2.22 (s, 3H), 1.15 (t, 3H).

25 Description 39

2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole

The title compound was prepared from 1-acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole (D38) using a similar procedure to Description 34.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.90 (s, 1H), 6.27 (s, 1H), 4.01 (t, 2H), 3.65 (br s, 1H), 3.53 (t, 2H), 2.95 (t, 2H), 2.74 (t, 2H), 2.53 (q, 2H), 2.34 (s, 6H), 1.14 (t, 3H).
30

Description 40

2,3-Dihydro-6-(2-dimethylaminoethoxy)-1H-indole

The title compound was prepared from 1-acetyl-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D32) using a similar procedure to Description 34 as an orange oil (17%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 6.97 (d, 1H), 6.28 - 6.22 (m, 2H), 4.01 (t, 2H), 3.74 (br s, 1H), 3.55 (t, 2H), 2.95 (t, 2H), 2.69 (t, 2H), 2.32 (s, 6H).

5

Description 41

4-Iodo-3-(1-methyl-piperidin-4-yloxy)acetanilide

3-Hydroxy-4-iodoacetanilide (5g, 18 mmole) in dry THF (100ml) was treated at room temperature with 4-hydroxy-1-methylpiperidine (2g, 18 mmole), triphenylphosphine (4.55g, 18 mmole) and diethylazodicarboxylate (3.132g, 18 mmole) at room temperature under an atmosphere of argon for 4h. The reaction mixture was concentrated *in vacuo* to a gum which was partitioned between dichloromethane and 5N hydrochloric acid. The aqueous phase was separated and adjusted to pH 11 with potassium carbonate. The product was recovered by extraction into dichloromethane, which was dried over sodium sulphate and concentrated *in vacuo* to give the title compound as a gum (4.4g, 65%).

10

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.65 (d, 1H), 7.5 (s, 1H), 7.45 (d, 1H), 6.6 (dd, 1H), 4.45 (m, 1H), 2.7 (m, 2H), 2.4 (m, 2H), 2.35 (s, 3H), 2.15 (s, 3H), 1.9 (m, 4H).

15

Description 42

4-Chloro-3-(1-methyl-piperidin-4-yloxy)-1-nitrobenzene

The title compound was prepared from 2-chloro-5-nitrophenol and 4-hydroxy-1-methylpiperidine using a similar procedure to description 41 to give the title compound in 26% yield.

20

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.8 (m, 2H), 7.5 (d, 1H), 4.5 (m, 1H), 2.7 (m, 2H), 2.45 (m, 2H), 2.35 (s, 3H), 2.0 (m, 4H).

25

Description 43

4-Chloro-3-(1-methyl-piperidin-4-yloxy)aniline

4-Chloro-3-(1-methyl-piperidin-4-yloxy)-1-nitrobenzene (D42, 2g, 7.4 mmole) in ethanol (50ml) was treated with tin (II) chloride (5.6g, 29.6 mmole) and conc. hydrochloric acid (10ml) and the reaction heated to reflux under an atmosphere of argon for 1.5h. The reaction was then concentrated *in vacuo* to a gum which was partitioned between dichloromethane and 40% aqueous sodium hydroxide solution. The dichloromethane

30

solution was separated, dried over sodium sulphate and concentrated *in vacuo* to a gum which was chromatographed on silica in a gradient of 5-15% methanol in dichloromethane. The title compound eluted in 10% methanol to give a colourless oil (710mg, 45%) which crystallised on standing.

- 5 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 7.1 (d, 1H), 6.3 (d, 1H), 6.25 (dd, 1H), 4.3 (m, 1H), 3.65 (br s, 2H), 2.7 (m, 2H), 2.35 (m, 2H), 2.3 (s, 3H), 1.95 (m, 4H).

Description 44

4-Bromo-3-hydroxyacetanilide

- 10 3-Hydroxyacetanilide (15.1g, 0.1 mole) in acetic acid (150ml) was treated with bromine (16.1g, 0.1 mole) in acetic acid (20ml) dropwise at room temperature with stirring. The reaction was allowed to stand at room temperature for 18h when the title compound (11.39g, 49%) was collected by filtration and dried *in vacuo*.

- 15 ^1H NMR (250 MHz, d^6DMSO) δ (ppm): 9.85 (s, 1H), 7.4 (s, 1H), 7.2 (d, 1H), 6.8 (dd, 1H), 1.9 (s, 3H). 1 proton not observed.

Description 45

4-Bromo-3-(2-dimethylaminoethoxy)acetanilide

- 20 The title compound was prepared from 4-bromo-3-hydroxyacetanilide and 2-dimethylaminoethyl chloride hydrochloride using a similar procedure to description 13 to afford the title compound in 46% yield.

^1H NMR (250 MHz, CDCl_3) δ (ppm): 7.8 (s, 1H), 7.5 (d, 1H), 7.4 (d, 1H), 6.75 (dd, 1H), 4.1 (t, 2H), 2.8 (t, 2H), 2.4 (s, 6H), 2.15 (s, 3H).

25 Description 46

4-Bromo-3-(2-dimethylaminoethoxy)aniline

- The title compound was prepared from 4-bromo-3-(2-dimethylaminoethoxy)acetanilide (D45) using a similar procedure to description 14 to give the title compound in 93% yield.

- 30 ^1H NMR (250 MHz, CDCl_3) δ (ppm): 7.2 (d, 1H), 6.25 (s, 1H), 6.15 (dd, 1H), 4.05 (t, 2H), 3.75 (s, 2H), 2.8 (t, 2H), 2.35 (s, 6H).

Description 47

1-Butyryl-2,3-dihydro-6-nitro-1H- indole

2,3-Dihydro-6-nitro-1-H-indole (16.4g, 100 mmole), in dichloromethane (200ml) was treated with butyryl chloride (10.6g, 100 mmole) and Et₃N (10.1g, 100 mmole) with continuous stirring at room temperature for 2h. The reaction was then washed

- 5 successively with 5N hydrochloric acid and saturated aqueous potassium carbonate solution. The reaction was then dried over sodium sulphate and concentrated *in vacuo* to a gum which crystallised from petrol as needles to give the title compound (23.4g, 100%).
¹H NMR (250 MHz, CDCl₃) δ (ppm): 9.0 (s, 1H), 7.85 (dd, 1H), 7.25 (d, 1H), 4.15 (t, 2H), 3.3 (t, 2H), 2.4 (t, 2H), 1.8 (q, 2H), 1.0 (t, 3H).

10

Description 48**6-Amino-1-butyryl-2,3-dihydro-1H-indole**

1-Butyryl-2,3-dihydro-6-nitro-1H-indole (D47) (19.8g, 84.4 mmole) was stirred with 10% palladium on charcoal (2g) in methanol (200ml) under an atmosphere of hydrogen at
15 50psi at such a rate that the temperature rose to 60°C and the uptake of hydrogen ceased. The reaction was then filtered through celite and the celite washed with hot methanol to ensure that no product was retained. The solutions were evaporated in vacuo to give the title compound (13.3g, 77%) as needles.

- 20 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.5 (s, 1H), 6.85 (d, 1H), 6.2 (dd, 1H), 4.9 (s, 2H), 4.0 (t, 2H), 2.9 (t, 2H), 2.4 (t, 2H), 1.6 (q, 2H), 0.95 (t, 3H).

Description 49**1-Butyryl-2,3-dihydro-6-hydroxy-1-H-indoline**

- 25 6-Amino-1-butyryl-2,3-dihydro-1H-indoline (D48, 20.4g, 100 mmole) in 1N sulphuric acid (300ml) was treated with sodium nitrite (6.9g, 100 mmole) at 0°C for 15min. The reaction was then poured into a boiling solution of copper (II) sulphate (25g) in water 150ml and held at 100°C for 15 min. The reaction was then cooled to RT and the slurry filtered to give the title compound (19.4g, 95%) as a brown powder.

- 30 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 9.2 (s, 1H), 7.65 (d, 1H), 6.95 (d, 1H), 6.4 (dd, 1H), 4.05 (t, 2H), 3.0 (t, 2H), 2.4 (t, 2H), 1.6 (q, 2H), 0.95 (t, 3H).

Description 50**5-Bromo-1-butyryl-2,3-dihydro-6-hydroxy-1H-indole**

- 1-Butyryl-2,3-dihydro-6-hydroxy-1H-indole (D49) (19.4g, 0.0946 moles) in methanol (1.5L) was treated with bromine (15.14g, 0.0946 mole) at room temperature for 0.5h. The reaction was then concentrated *in vacuo* to a gum which was triturated with ether/methanol when the title compound crystallised as needles and was collected by filtration (17.48g, 65%).
- ¹H NMR (250 Mhz, d⁶DMSO) δ (ppm): 10.05 (br s, 1H), 7.85 (s, 1H), 7.25 (s, 1H), 4.05 (t, 2H), 3. (t, 2H), 2.45 (t, 2H), 1.6 (q, 2H), 0.8 (t, 3H).

Description 51

- 5-Bromo-1-butyryl-2,3-dihydro-6-(1-methyl-piperidin-4-yloxy)-1H-indole
- The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-hydroxy-1H-indole (D50) and 1-hydroxy-4-methylpiperidine using a similar procedure to Description 41 as needles (62%).
- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.0 (s, 1H), 7.3 (s, 1H), 4.5 (m, 1H), 4.1 (t, 2H), 3.1 (t, 2H), 2.7 (m, 2H), 2.4 (m, 4H), 2.3 (s, 3H), 2.0 (m, 4H), 1.75 (q, 2H), 1.0 (t, 3H).

Description 52

- 5-Bromo-2,3-dihydro-6-(1-methyl-piperidin-4-yloxy)-1H-indole
- 5-Bromo-1-butyryl-2,3-dihydro-6-(1-methyl-piperidin-4-yloxy)-1H-indole (D51, 380mg, 1 mmole) was dissolved in 2M HBr and heated under reflux for 0.5h when the reaction was cooled and neutralised with saturated aqueous potassium carbonate solution and the product recovered by extraction into dichloromethane. The dichloromethane solution was dried over sodium sulphate and concentrated *in vacuo* to give the title compound 300mg, (100%).
- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.2 (s, 1H), 6.3 (s, 1H), 4.25 (m, 1H), 3.8 (s, 1H), 3.6 (s, 2H), 3.0 (t, 2H), 2.7 (m, 2H), 2.45 (m, 2H), 2.3 (s, 3H), 1.95 (m, 4H).

Description 53

- 4-(Pyridin-4-yl)-3-trifluoromethylacetanilide
- The title compound was prepared from 4-bromo-3-trifluoromethylacetanilide and 4-pyridylboronic acid using a similar procedure to Description 3 as crystalline needles from ether (59%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (m, 2H), 8.4 (s, 1H), 7.9 (m, 2H), 7.3 (m, 3H), 2.25 (s, 3H).

Description 54

5 4-(Pyridin-4-yl)-3-trifluoromethylaniline

The title compound was prepared from 4-(pyridin-4-yl)-3-trifluoromethylacetanilide (D53) in a similar manner to description 26 in 95% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.6 (m, 2H), 7.25 (m, 2H), 7.05 (m, 2H), 6.85 (m, 1H), 4.0 (s, 2H).

10

Description 55

4-Chloro-3-(2-dimethylaminoethoxy)-1-nitrobenzene

The title compound was prepared from 2-chloro-5-nitrophenol and 2-dimethylaminoethyl chloride hydrochloride using a similar procedure to Description 25 as needles (36%).

15 ¹H NMR (250MHz, CDCl₃) δ (ppm): 7.8 (m, 2H), 7.5 (m, 1H), 4.25 (t, 2H), 2.9 (t, 2H), 2.4 (s, 6H).

Description 56

4-Chloro-3-(2-dimethylaminoethoxy)aniline

20 The title compound was prepared from 4-chloro-3-(2-dimethylaminoethoxy)-1-nitrobenzene (D55) using a similar procedure to Description 43 (83%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.1 (d, 1H), 6.3 (d, 1H), 6.2 (dd, 1H), 4.1 (t, 2H), 3.7 (s, 2H), 2.8 (t, 2H), 2.35 (s, 6H).

25 Description 57

5-Bromo-1-butyryl-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole

The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-hydroxy-1H-indole (D50) and (1-methylpiperidin-3-yl)methanol following a similar procedure to Description 41 to give the title compound in 49% yield which crystallised on standing.

30 m.p. 100-102°C.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.0 (s, 1H), 7.25 (s, 1H), 4.05 (t, 2H), 4.0-3.8 (m, 2H), 3.1 (t, 2H), 3.05 (m, 1H), 2.8 (m, 1H), 2.35 (t, 2H), 2.3 (s, 3H), 2.25-1.65 (m, 6H), 1.75 (q, 2H), 1.3-1.1 (m, 1H), 1.05 (t, 3H).

5 **Description 58**

5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole

The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole (D57) following a similar procedure to Description 52 to give the title compound which crystallised from ether as needles. m.p.

10 112-115°C in 57% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.2 (s, 1H), 6.25 (s, 1H), 3.8 (m, 2H), 3.55 (t, 2H), 3.0 (br s, 1H), 2.95 (t, 2H), 2.75 (m, 1H), 2.3 (s, 3H), 2.2 (m, 1H), 2.05-1.55 (m, 6H), 1.2-1.05 (m, 1H).

15 **Description 59**

5-Bromo-1-butyryl-6-2,3-dihydro-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole(a) and 5-Bromo-1-butyryl-2,3-dihydro-6-[(1-methylpiperidin-3-yl)oxy]-1H-indole (b)

Reaction of 5-bromo-1-butyryl-2,3-dihydro-6-hydroxy-1H-indole (D50) and (1-methylpyrrolidin-2-yl)methanol following a similar procedure to description 41 gave a mixture of the title compound (a) and the title compound (b). Chromatography on silica in 7-10% methanol in CH₂Cl₂ gave the title compound (a) in 44% yield from the first fraction, and the second fraction afforded the title compound (b) in 25% yield which crystallised on standing. m.p. 70-74°C.

Title compound (a):

25 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.0 (s, 1H), 7.3 (s, 1H), 4.25-4.0 (m, 4H), 3.2-3.0 (t, 2H), 2.6 (s, 3H), 2.45-2.25 (m, 3H), 2.15-1.65 (m, 4H), 1.3 (t, 4H), 1.0 (t, 3H).

Title compound (b):

30 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.05 (s, 1H), 7.25 (s, 1H), 4.35 (m, 2H), 4.05 (t, 2H), 3.1 (t, 2H), 3.0 (m, 1H), 2.6 (m, 1H), 2.35 (t, 1H), 2.25 (s, 3H), 1.75 (q, 2H), 2.2-1.4 (m, 4H), 1.0 (t, 3H), 0.85 (m, 2H).

Description 60

5-Bromo-2,3-dihydro-6-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole

The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole (D59a) following a similar procedure to Description 52 to give the title compound in 95% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.15 (s, 1H), 6.25 (s, 1H), 4.2 (br s, 1H), 3.95 (m, 1H), 3.8 (m, 1H), 3.55 (t, 2H), 3.1 (m, 1H), 2.95 (t, 2H), 2.7 (m, 1H), 2.55 (s, 3H), 2.3 (m, 1H), 2.1 (m, 1H), 1.9-1.55 (m, 3H).

Description 61

5-Bromo-2,3-dihydro 6-[(1-methylpiperidin-3-yl)oxy]-1H-indole

The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-[(1-methylpiperidin-3-yl)oxy]-1H-indole (D59b) following a similar procedure to description 52 to give the title compound as a gum.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.2 (s, 1H), 6.35 (s, 1H), 4.2 (m, 1H), 3.75 (br s, 1H), 3.55 (t, 2H), 3.05 (m, 1H), 2.95 (t, 2H), 2.7 (m, 1H), 2.3 (s, 3H), 2.2-1.9 (m, 3H), 1.8 (m, 1H), 1.6 (m, 1H), 1.5 (m, 1H).

Description 62

5-Bromo-1-butyryl-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole

The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-hydroxy-1H-indole (D50) and (1-methylpiperidin-4-yl)methanol following a similar procedure to description 41 to give the title compound as cubes (m.p. 114-115°C) in 75% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.0 (s, 1H), 7.3 (s, 1H), 4.1 (t, 2H), 3.9 (d, 2H), 3.1 (t, 2H), 2.9 (m, 2H), 2.4 (t, 2H), 2.25 (s, 3H), 2.05-1.65 (m, 7H), 1.45 (m, 2H), 1.05 (t, 3H).

Description 63

5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole

The title compound was prepared from 5-bromo-1-butyryl-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole (D62) following a similar procedure to Description 52 to give the title compound as needles from ether (m.p. 109-112°C) in 61% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.2 (s, 1H), 6.25 (s, 1H), 3.75 (d, 2H), 3.55 (t, 2H), 2.95 (t, 2H), 2.85 (m, 2H), 2.25 (s, 3H), 2.0-1.7 (m, 6H), 1.5-1.3 (m, 2H).

Description 64**5-(Pyridin-4-yl)-1-naphthoic acid**

The title compound was prepared from 5-bromo-1-naphthoic acid (EP 547442 A1) and 4-pyridylboronic acid using a similar procedure to Description 3.

¹H NMR (250 MHz, d⁶DMSO) δ (ppm): 8.75 (d, 1H), 8.56 (dd, 2H), 7.98 (d, 1H), 7.78 (d, 1H), 7.56 (t, 1H), 7.45-7.34 (m, 4H). COOH not observed.

Description 65**5-(Pyridin-4-yl)naphth-1-ylisocyanate**

The title compound was prepared from 5-(pyridin-4-yl)-1-naphthoic acid (D64) using a similar procedure to Description 1.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.74 (d, 2H), 8.21 (d, 1H), 7.69-7.61 (m, 2H), 7.49-7.33 (m, 5H).

Description 66**3-(2,3-Dihydro-1-H-indol-6-yl)-N,N,-dimethylacrylamide**

A stirred solution of 2,3-dihydro-6-iodo-1H-indole (20g, 0.08 mole, Heterocycles 1987, 26 (11) 2817) and N,N-dimethylacrylamide (9.3ml, 0.09 mole) in a mixture of dry dimethylformamide (60ml) and triethylamine (29ml, 0.21 mole) was degassed by bubbling argon through for 0.5h. Palladium (II) acetate (368mg, 1.64mmole) and tri-*o*-tolylphosphine (2.0g, 6.6 mmole) were added and the mixture stirred. A rapid exotherm was observed climbing through 70°C in approx. 5 min. and the reaction vessel was immersed in an ice water bath while stirring for 30 min. On cooling to room temperature, water (50ml) was added and the product extracted with dichloromethane (x2). The combined organics were washed with water (x3), dried (Na₂SO₄) and evaporated *in vacuo* to a brown solid. Recrystallisation from ethyl acetate/diethyl ether gave the title compound as a crystalline brown solid (9.2g, 52%).

¹H NMR (250MHz, CDCl₃) δ(ppm): 7.58 (d, 1H), 7.09 (d, 1H), 6.88 (dd, 1H), 6.80 (s, 1H), 6.79 (d, 1H), 3.58 (t, 2H), 3.15 (s, 3H), 3.06 (s, 3H), 3.03 (t, 2H). NH not observed.

Description 67**3-(2,3-Dihydro-1H-indol-6-yl)-N,N-dimethylpropylamide**

3-(2,3-Dihydro-1H-indol-6-yl)-N,N-dimethylacrylamide (D66 , 9.1g, 0.042mole) in ethanol (200ml) was hydrogenated over 10% palladium on charcoal at 50 psi and 50°C for 100 h. Filtration of the mixture and evaporation of the filtrate *in vacuo* gave the title compound as a white solid (8.3g, 91%).

- 5 ¹H NMR (250MHz,CDCl₃) δ(ppm): 7.02 (d, 1H), 6.55 (m, 2H), 3.54 (t, 2H), 2.99 (t, 2H), 2.95 (s, 3H), 2.94 (s, 3H), 2.86 (t, 2H), 2.57 (t, 2H). NH not observed.

Description 68

2,3-Dihydro-6-(3-dimethylaminopropyl)-1H-indole

- 10 3-(2,3-Dihydro-1H-indol-6-yl)-N,N-dimethylpropylamide (D67 , 8.3g, 0.038mol) was dissolved in dry tetrahydrofuran (400ml), cooled to 0°C and treated portionwise with lithium aluminium hydride (2.16g, 0.057mole). The mixture was stirred at room temperature for 4h, then water (3.5ml), then 10% aqueous sodium hydroxide (3.5ml) and then water (10.5ml) were added sequentially and the mixture filtered. The filtrate was
- 15 evaporated *in vacuo* to give the title compound as an orange oil (7.3g, 94%).

¹H NMR (250MHz,CDCl₃) δ(ppm): 7.02 (d, 1H), 6.53 (d, 1H), 6.51 (s, 1H), 3.72 (br s, 1H), 3.54 (t, 2H), 2.99 (t, 2H), 2.53 (t, 2H), 2.29 (t, 2H), 2.22 (s, 6H), 1.78 (m, 2H).

Description 69

- 20 1-Acetyl-2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole

To a stirred solution of 2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole (D68 , 4.0g, 0.020mole) in dichloromethane (50ml) containing triethylamine (4.2ml, 0.030mole) was added dropwise a solution of acetyl chloride (1.6ml, 0.023mole) in dichloromethane (10ml). The mixture was stirred for 18h, washed with aqueous 10% sodium carbonate,

25 the organics dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a brown oil (4.5g, 91%).

¹H NMR (250MHz,CDCl₃) δ(ppm): 8.09 (s, 1H), 7.08 (d, 1H), 6.86 (dd, 1H), 4.05 (t, 2H), 3.15 (t, 2H), 2.62 (t, 2H), 2.30 (t, 2H), 2.22 (s, 9H), 1.79 (m, 2H).

- 30 Description 70

5-Chloro-2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole

To a stirred solution of 1-acetyl-2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole (D69 , 500mg, 2.0mmole) in acetic acid (5ml) was added N-chlorosuccinimide (467mg,

3.5mmol) and the mixture stirred at room temperature for 24h. Evaporation *in vacuo* and purification with flash chromatography afforded a yellow solid (100mg) which was stirred in 2M HCl (20ml) and ethanol (2 drops) at 80°C for 3h. On cooling, the mixture was basified with solid K₂CO₃, the product extracted with dichloromethane (2x), dried
5 (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a brown oil (70mg, 15%).

¹H NMR (250MHz, CDCl₃) δ(ppm): 7.05 (s, 1H), 6.50 (s, 1H), 3.55 (t, 2H), 2.98 (t, 2H), 2.63 (t, 2H), 2.32 (t, 2H), 2.24 (s, 6H), 1.74 (m, 2H). NH not observed.

10 Description 71

2,3-Dihydro-5-iodo-6-(3-dimethylaminopropyl)-1H-indole

The title compound was prepared from 1-acetyl-2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole (D69) and N-iodosuccinimide using a similar procedure to Description 70 (8%).

15 ¹H NMR (250MHz, CDCl₃) δ(ppm): 7.47 (s, 1H), 6.55 (s, 1H), 3.55 (t, 2H), 2.98 (t, 2H), 2.61 (t, 2H), 2.33 (t, 2H), 2.24 (s, 6H), 1.73 (m, 2H). NH not observed.

Description 72

2,3-Dichloro-4-(pyridin-4-yl)aniline

20 4-Bromo-2,3-dichloroacetanilide was reacted with 4-pyridylboronic acid using a similar procedure to Description 3 to afford 2,3-dichloro-4-(pyridin-4-yl)acetanilide; which was hydrolysed by heating with 2M NaOH and EtOH for 36h, to afford the title compound as an orange solid.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.64 (d, 2H), 7.32 (d, 2H), 7.05 (d, 1H), 6.85 (d, 25 1H), 4.40 (br s, 2H).

Description 73

1-Benzoyl-2,3-dihydro-6-nitro-1H-indole

A stirred solution of 2,3-dihydro-6-nitro-1H-indole (20g, 0.12 mole) and triethylamine
30 (28ml, 0.20 mole) in dichloromethane (300ml) at 0°C was treated dropwise over 15 minutes with a solution of benzoyl chloride (15.5ml, 0.13 mole) in dichloromethane (25ml). The mixture was allowed to warm to room temperature and stir for 2 hours, then treated with 5% Na₂CO₃ solution (200ml), stirred for 1 hour, then the dichloromethane

layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a yellow solid (34.3g, 100%).

^1H NMR (250MHz, CDCl_3) δ (ppm): 7.92 (dd, 1H), 7.61 - 7.42 (m, 6H), 7.32 (d, 1H), 4.18 (t, 2H), 3.22 (t, 2H).

5

Description 74

6-Amino-1-benzoyl-2,3-dihydro-1H-indole

A solution of 1-benzoyl-2,3-dihydro-6-nitro-1H-indole (D73, 34g, 0.12 mole) in THF (1000ml) was hydrogenated over 10% Pd-C (6g) at atmospheric temperature and pressure until uptake of hydrogen ceased. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo* to afford the title compound as a beige solid (28.9g, 100%).

10

^1H NMR (250 MHz, CDCl_3) δ (ppm): 7.25 - 7.05 (m, 6H), 6.60 (d, 1H), 6.02 (d, 1H), 3.80 (br s, 2H), 3.65 (t, 2H), 2.63 (t, 2H).

15

Description 75

1-Benzoyl-2,3-dihydro-6-iodo-1H-indole

A stirred suspension of 6-amino-1-benzoyl-2,3-dihydro-1H-indole (D74, 8.2g, 0.034 mole) in a mixture of conc. H_2SO_4 acid (4.5ml) and water (70ml) at 2°C was treated dropwise over 15 minutes with a solution of sodium nitrite (2.56g, 0.037 mole) in water (20ml). The reaction mixture was stirred at $3-4^\circ\text{C}$ for 45 minutes, then added portionwise over 5 minutes to a stirred solution of potassium iodide (6.28g, 0.038 mole) in water (25ml) at 5°C . The mixture was allowed to warm to room temperature for 3 hours, then extracted with ethyl acetate and the extract washed with aqueous Na_2SO_3 solution, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a brown solid (10.6g, 89%).

20

25

^1H NMR (250 MHz, CDCl_3) δ (ppm): 7.58 - 7.42 (m, 6H), 7.36 (d, 1H), 6.94 (d, 1H), 4.05 (t, 2H), 3.06 (t, 2H).

30

Description 76

1-Benzyl-2,3-dihydro-6-iodo-1H-indole

A stirred solution of 1-benzoyl-2,3-dihydro-6-iodo-1H-indole (D75, 7.1g, 0.020 mole) in dry THF (140 ml) at room temperature under argon was treated dropwise over 10 minutes

with 1M borane-THF complex in THF (40ml, 0.040 mole), then heated under reflux for 2 hours. The solution was allowed to cool, treated cautiously with 1M HCl acid (40ml), stirred for 20 minutes, then basified with solid K_2CO_3 and concentrated *in vacuo*. The residue was extracted with ethyl acetate and the extract dried (Na_2SO_4) and concentrated *in vacuo*, to afford a yellow oil (6.9g). This was dissolved in acetone (200ml), treated with anhydrous K_2CO_3 (2.76g) and benzyl bromide (1.2ml) and heated under reflux for 5 hours, then concentrated *in vacuo* and the residue treated with water (150ml) and extracted with ethyl acetate. The extract was dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with 0-20% ether/60-80 petrol to afford the title compound as a pale yellow solid (6.18g, 91%).
 1H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.40 - 7.22 (m, 5H), 6.96 (dd, 1H), 6.85 - 6.78 (m, 2H), 4.22 (s, 2H), 3.32 (t, 2H), 2.92 (t, 2H).

Description 77

15 N-Methoxy-N-methyl-1-methylpiperidin-4-yl carboxamide

A stirred suspension of 1-methylpiperidin-4-yl carboxylic acid (4.4g, 0.031 mole) in thionyl chloride (60ml) was heated under reflux for 1 hour, then concentrated *in vacuo* to afford the acid chloride as a yellow solid. This was dissolved in chloroform (100ml) and added dropwise over 5 minutes to a stirred suspension of N,O-dimethylhydroxylamine hydrochloride (3.4g, 0.035 mole) and pyridine (6.1ml, 0.075 mole) in chloroform (300ml). The mixture was stirred at room temperature for 3 hours, then washed with 10% Na_2CO_3 solution (100ml), dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a yellow oil (3.92g, 68%).

1H NMR (250MHz, $CDCl_3$) δ (ppm): 3.70 (s, 3H), 3.18 (s, 3H), 2.91 (br d, 2H), 2.72 - 2.56 (m, 1H), 2.27 (s, 3H), 2.06 - 1.70 (m, 6H).

Description 78

1-Benzyl-2,3-6-[(1-methylpiperidin-4-yl)carbonyl]-1H-indole

A stirred solution of 1-benzyl-2,3-dihydro-6-iodo-1H-indole (D76, 1.0g, 0.003 mole) in dry THF (30ml) at $-65^\circ C$ under argon was treated with 1.6M n-butyllithium in hexane (1.9ml, 0.003 mole). The solution was stirred at $-60^\circ C$ for 10 minutes then a solution of N-methoxy-N-methyl-1-methylpiperidin-4-ylcarboxamide (D77, 0.56g, 0.003 mole) in dry THF (15ml) was added and the mixture allowed to warm to room temperature and stir

for 2 hours. The solution was treated with 1M HCl acid (25ml), stirred for 5 minutes, then basified by addition of solid K_2CO_3 and extracted with ethyl acetate. The extract was dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by chromatography on silica gel eluting with ether, then with 10% methanol/ethyl acetate to afford the title compound as an orange solid (0.38g, 38%).

1H NMR (250MHz, $CDCl_3$) δ (ppm): 7.40 - 7.22 (m, 6H), 7.12 (d, 1H), 7.03 (d, 1H), 4.30 (s, 2H), 3.38 (t, 2H), 3.22 - 3.08 (m, 1H), 3.04 (t, 2H), 3.00 - 2.87 (m, 2H), 2.31 (s, 3H), 2.16 - 2.03 (m, 2H), 1.90 - 1.80 (m, 4H).

10 Description 79

1-Benzyl-2,3-dihydro-6-[1-hydroxy-1-(1-methylpiperidin-4-yl)methyl]-1H-indole

A stirred solution of 1-benzyl-2,3-dihydro-6-[(1-methylpiperidin-4-yl)carbonyl]-1H-indole (D78, 1.7g, 0.0051 mole) in ethanol (80ml) at room temperature under argon was treated portionwise over 5 minutes with sodium borohydride (0.38g, 0.010 mole). The mixture was stirred for 2 hours, then treated with 10% Na_2CO_3 solution (15ml), stirred for a further 20 minutes, then concentrated under vacuum to approx. 25ml volume and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford a yellow oil (1.45g) containing the title compound.

1H NMR (250MHz, $CDCl_3$) δ (ppm): 7.40 - 7.25 (m, 5H), 7.04 (d, 1H), 6.58 (dd, 1H), 6.50 (s, 1H), 4.27 (s, 2H), 4.24 (d, 1H), 3.31 (t, 2H), 2.94 (t, 2H), 2.95 - 2.72 (m, 3H), 2.23 (s, 3H), 2.05 - 1.30 (m, 6H). OH not discernible.

Description 80

1-Acetyl-2,3-dihydro-6-[1-hydroxy-1-(1-methylpiperidin-4-yl)methyl]-1H-indole

A stirred solution of 1-benzyl-2,3-dihydro-6-[1-hydroxy-1-(1-methylpiperidin-4-yl)methyl]-1H-indole (D79, 1.3g, 0.0039 mole) in ethanol (80ml) and acetic acid (5ml) was hydrogenated over 10% Pd-C (0.3g) at 45°C and 40 psi for 20 hours. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated under vacuum. The residue was dissolved in dichloromethane (30ml), treated with acetic anhydride (0.5ml, 0.009 mole) and stirred at room temperature for 40 minutes. The mixture was treated with 10% Na_2CO_3 solution (20ml), stirred well for 20 minutes, then extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale yellow oil (0.85g, 76%). MH^+ 289.

Description 81**1-Acetyl-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1H-indole**

A stirred solution of 1-acetyl-2,3-dihydro-6-[1-hydroxy-1-(1-methylpiperidin-4-yl)methyl]-1H-indole (D80, 0.85g, 0.0030 mole) in trifluoroacetic acid (12ml) was treated with triethylsilane (2.4ml, 0.015 mole) and stirred well at room temperature for 24 hours, then allowed to stand for 12 days. The mixture was diluted with water (50ml), basified by addition of solid K_2CO_3 and extracted with dichloromethane. The extract was dried (Na_2SO_4), concentrated under vacuum and the residue crystallised from ethyl acetate to afford the title compound as a beige solid (170mg, 21%).

1H NMR (250MHz, $CDCl_3$) δ (ppm): 8.03 (d, 1H), 7.07 (d, 1H), 6.80 (dd, 1H), 4.05 (t, 2H), 3.15 (t, 2H), 2.85 - 2.75 (m, 2H), 2.52 (d, 2H), 2.22 (s, 6H), 1.90 - 1.78 (m, 2H), 1.70 - 1.58 (m, 2H), 1.58 - 1.40 (m, 1H), 1.38 - 1.22 (m, 2H).

Description 82**1-Acetyl-5-bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1H-indole**

The title compound was prepared from 1-acetyl-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1H-indole (D81) and N-bromosuccinimide using a similar procedure to Description 33 as a beige solid (92%).

1H NMR (250MHz, $CDCl_3$) δ (ppm): 8.07 (s, 1H), 7.32 (s, 1H), 4.05 (t, 2H), 3.15 (t, 2H), 2.88 - 2.78 (m, 2H), 2.65 (d, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 1.85 (td, 2H), 1.70 - 1.50 (m, 3H), 1.50 - 1.30 (m, 2H).

Description 83**5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1H-indole**

The title compound was prepared from 1-acetyl-5-bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1H-indole (D82) using a similar procedure to Description 34 as a pale yellow gum (91%).

1H NMR (250MHz, $CDCl_3$) δ (ppm): 7.23 (s, 1H), 6.44 (s, 1H), 3.72 (br s, 1H), 3.55 (t, 2H), 2.99 (t, 2H), 2.85 - 2.75 (m, 2H), 2.54 (d, 2H), 2.23 (s, 3H), 1.84 (td, 2H), 1.73 - 1.50 (m, 3H), 1.45 - 1.25 (m, 2H).

Description 84

***E*-1-Benzoyl-2,3-dihydro-6-[2-(pyridin-2-yl)ethenyl]-1H-indole**

To a stirred solution of 1-benzoyl-2,3-dihydro-6-iodo-1H-indole (D75, 2.53g, 7.2 mmole) in acetonitrile (80ml) were added palladium (II) acetate (0.08g, 0.36 mmole), tri (o-tolyl)phosphine (0.44g, 1.45 mmole) and 2-vinylpyridine (0.76g, 7.2 mmole). The mixture was degassed by bubbling with argon for 20 min, NEt₃ (1.83g, 18 mmole) was added and the mixture was heated at reflux under argon for 18h, then allowed to cool and the solvent removed *in vacuo*. The residue was partitioned between CH₂Cl₂ and 5% Na₂CO₃ (aq), the organic layer separated, dried (Na₂SO₄) and concentrated *in vacuo* giving a dark brown oil, which was crystallised from EtOAc, affording the title compound as a beige solid (1.51g, 64%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.59 (d, 1H), 7.65 - 7.39 (m, 7H), 7.31 - 7.11 (m, 6H), 4.11 (br s, 2H), 3.13 (t, 2H).

Description 85**1-Benzoyl-2,3-dihydro-6-[2-(pyridin-2-yl)ethyl]-1-indole**

A solution of *E*-1-benzoyl-2,3-dihydro-6-[2-(pyridin-2-yl)ethenyl]-1H-indole (D84, 1.50g, 4.6 mmole) in EtOH (80ml) and AcOH (20ml) was hydrogenated over 10% Pd/C catalyst at room temperature and pressure. After 80h the catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ and 10% Na₂CO₃ (aq), the organic layer separated, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a yellow oil (1.37g, 91%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.54 (d, 1H), 7.60 - 7.40 (m, 7H), 7.13 - 7.08 (m, 3H), 6.86 (d, 1H), 4.07 (br s, 2H), 3.07 (t, 2H), 3.10 - 3.03 (m, 4H).

Description 86**1-Benzoyl-2,3-dihydro-6-[2-(1-methyl-2-pyridinium)ethyl]-1H-indole iodide salt**

A solution of 1-benzoyl-2,3-dihydro-6-[2-(pyridin-2-yl)ethyl]-1-H-indole (D85, 1.35g, 4.1 mmole) in acetone (30ml) was treated with methyl iodide (0.51ml, 8.2 mmole), stirred briefly to mix, then left to stand for 4 days. The acetone and excess methyl iodide were removed *in vacuo* leaving the title compound as a brown oil (1.93g, 100%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.73 (d, 1H), 8.42 - 8.31 (m, 2H), 7.80 (dt, 1H), 7.56 - 7.45 (m, 6H), 7.12 (d, 1H), 6.85 (d, 1H), 4.07 (s, 3H), 4.02 (t, 2H), 3.50 - 3.35 (m, 2H), 3.11 - 3.04 (m, 4H).

Description 87**1-Benzoyl-2,3-dihydro-6-[2-(1-methyl-1,2,5,6-tetrahydropiperidin-2-yl)ethyl]-1H-indole**

- 5 A stirred solution of 1-benzoyl-2,3-dihydro-6-[2-(1-methyl-2-pyridinium)ethyl]-1H-indole iodide salt (D86, 1.90g, 4.0 mmole) in EtOH (30ml), MeOH (20ml) and H₂O (40ml) was cooled in ice, under argon, and treated portionwise over 5 min with sodium borohydride, (0.23g, 6.1 mmole). The mixture was stirred at 0°C for 30 min, then at room temperature for 2.5h, after which 10% NaOH (10ml) was added, followed by H₂O (20ml). The product was extracted into CH₂Cl₂ and the organic layer dried (Na₂SO₄) and concentrated *in vacuo* giving the title compound as an orange oil (1.36, 97%). MH⁺ 347. The material was used without further purification.

Description 88**1-Benzoyl-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole**

- 15 A solution of 1-benzoyl-2,3-dihydro-6-[2-(1-methyl-1,2,5,6-tetrahydropiperidin-2-yl)ethyl]-1H-indole (D87, 1.36g, 3.9 mmole) in EtOH (50ml) was hydrogenated over 10% Pd/C catalyst at room temperature and 50 psi (344.8KPa). After 44h the catalyst was filtered off and the filtrate concentrated *in vacuo* to afford a yellow brown oil, which was purified by column chromatography on basic alumina eluting with EtOAc to afford the title compound as a yellow oil (0.44g, 33%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.55 - 7.44 (m, 6H), 7.11 (d, 1H), 6.84 (br s, 1H), 4.08 (m, 2H), 3.08 (t, 2H), 2.84 (br d, 1H), 2.49 - 2.38 (m, 2H), 2.24 (s, 3H), 2.05 - 1.40 (m, 10H).

Description 89**2,3-Dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole**

- The title compound was prepared from 1-benzoyl-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole (D88), using a similar procedure to Description 34, as a brown oil (67%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.02 (d, 1H), 6.54 (d, 1H), 6.51 (d, 1H), 3.54 (t, 2H), 2.99 (t, 2H), 2.84 (br d, 1H), 2.27 (s, 3H), 2.00 - 1.50 (m, 12H). NH not discernible

Description 90**1-Acetyl-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole**

A stirred solution of 2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole (D89, 200mg, 0.82 mmole) in CH₂Cl₂ (30ml) was treated with acetic anhydride (92mg, 0.90 mmole) and stirred at room temperature for 3h. A solution of 10% Na₂CO₃ (20ml) was added and the mixture stirred vigorously for 20 mins, then the organic layer was separated, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a brown oil (234mg, 100%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.10 (s, 1H), 7.08 (d, 1H), 6.85 (d, 1H), 4.05 (t, 2H), 3.16 (t, 2H), 2.85 (br dt, 1H), 2.71 - 2.48 (m, 2H), 2.28 (s, 3H), 2.22 (s, 3H), 2.15 - 1.26 (m, 10H).

Description 91**1-Acetyl-5-bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole**

The title compound was prepared from 1-acetyl-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole (D90) and N-bromosuccinimide, using a similar procedure to Description 33, as a brown solid (79%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.12 (s, 1H), 7.31 (s, 1H), 4.06 (t, 2H), 3.15 (t, 2H), 2.85 - 2.66 (m, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 2.10 - 1.50 (m, 10H).

Description 92**5-Bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole**

The title compound was prepared from 1-acetyl-5-bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole (D91), using a similar procedure to Description 34, as a brown solid (75%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.21 (s, 1H), 6.51 (s, 1H), 3.70 (br s, 1H), 3.55 (t, 2H), 2.99 (t, 2H), 2.86 (br dd, 1H), 2.68 - 2.55 (m, 2H), 2.31 (s, 3H), 2.09 - 1.40 (m, 10H).

Example 1

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]urea

A stirred solution of 3-(2-dimethylaminoethoxy)-4-iodoaniline (215mg, 0.70mmole, Description 50 in WO 95/15954) in dichloromethane (20ml) was treated with a solution of 2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-isocyanate (D1, 200mg, 0.69 mmole) in dichloromethane (10ml). The stirred mixture was kept at 20°C for 20h. then concentrated *in vacuo* and the residue chromatographed on silica gel eluting with 0-5% methanol/dichloromethane to afford the title compound as a yellow solid (275mg, 67%). This was converted to its hydrochloride salt and crystallised from acetone/ether.

¹H NMR (free base) (250MHz, CDCl₃) δ (ppm): 8.00 (s, 1H), 7.94 (d, 1H), 7.85 (s, 1H), 7.77 (s, 1H), 7.58 (d, 1H), 7.45 (d, 2H), 7.33 - 7.24 (m, 3H), 7.19 (d, 1H), 6.65 (dd, 1H), 4.09 (t, 2H), 2.85 (t, 2H), 2.71 (s, 3H), 2.42 (s, 6H), 2.31 (s, 3H).

Example 2

N-[4-Bromo-3-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

The compound was prepared from 4-bromo-3-methylphenylisocyanate (D2) using a similar procedure to Example 1.

¹H NMR (250MHz, CDCl₃) δ (ppm): 7.78 (s, 1H), 7.66 (s, 1H), 7.52 (d, 1H), 7.37 (d, 1H), 7.14 (d, 1H), 7.05 (d, 1H), 6.96 (dd, 1H), 6.46 (dd, 1H), 4.00 (t, 2H), 2.79 (t, 2H), 2.39 (s, 6H), 2.29 (s, 3H).

Example 3

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]naphth-1-ylacetamide

Naphth-1-ylacetic acid (250mg, 1.34 mmole) was dissolved in dichloromethane (10ml) and treated with oxalyl chloride (338mg, 2.68 mmole) and dimethylformamide (1 drop) at room temperature and stirred under an atmosphere of argon for 2h. The reaction was then concentrated *in vacuo* to a gum which was azeotroped with dry toluene to remove the last traces of oxalyl chloride. The gum was dissolved in dichloromethane (30ml) and treated at room temperature with 3-(2-dimethylaminoethoxy)-4-iodoaniline (410mg, 1.34 mmole, D50 in WO 95/15954) and triethylamine (270mg, 2.68 mmole). After 2h the reaction was washed with aqueous potassium carbonate solution, dried (Na₂SO₄) and concentrated *in vacuo* to a gum, which was crystallised from ether to give the title compound as needles m.p. 135 - 137°C (410mg, 64%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.00 - 7.80 (m, 3H), 7.60 - 7.40 (m, 5H), 7.25 (s, 1H), 7.05 (s, 1H), 6.40 (d, 1H), 4.15 (s, 2H), 4.25 (t, 2H), 2.75 (t, 2H), 2.30 (s, 6H).

Example 4**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-4-bromophenyl carbamate**

5 The title compound was prepared from 4-bromophenyl chloroformate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) following a similar procedure to the coupling step of Example 3.

¹H NMR (HCl salt) (250MHz, d⁶DMSO) δ (ppm): 10.50 (brs, 1H), 10.41 (s, 1H), 7.62 (d, 1H), 7.53 (d, 2H), 7.28 (s, 1H), 7.14 (d, 2H), 6.90 (d, 1H), 4.32 (br s, 2H), 3.53 (br s, 2H), 2.89 (s, 6H).

10

Example 5**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[(2-trifluoromethyl)phenyl]urea**

The title compound was prepared from 2-trifluoromethylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

15

MS: m/z = 494 (MH⁺)

Example 6**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[(4-fluoro-3-nitro)phenyl]urea**

20 The title compound was prepared from 4-fluoro-3-nitrophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: m/z = 489 (MH⁺).

Example 7**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[4-phenoxyphenyl]urea**

25 The title compound was prepared from 4-phenoxyphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

30 ¹H NMR (HCl salt) (250MHz, d⁶DMSO) δ (ppm): 10.19 (br s, 1H), 9.21 (s, 1H), 9.07 (s, 1H), 7.48 (d, 1H), 7.40-7.30 (m, 2H), 7.20 (t, 2H), 6.93 (t, 1H), 6.85-6.75 (m, 4H), 6.64 (d, 1H), 4.22 (br s, 2H), 3.42 (br s, 2H), 2.78 (s, 3H), 2.77 (s, 3H).

Example 8**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-4-bromophenylacetamide**

The title compound was prepared from 4-bromophenylacetic acid and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) following a similar procedure to Example 3.

^1H NMR (250MHz, CDCl_3) δ (ppm): 8.26 (s, 1H), 7.45 (d, 2H), 7.32 (s, 1H), 7.00 (d, 2H), 6.55 (d, 1H), 3.88 (m, 2H), 3.45 (s, 2H), 2.65 (m, 2H), 2.25 (s, 6H).

Example 9**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea**

To a stirred solution of triphosgene (77mg, 0.26 mmole) in dichloromethane (10ml) was added a solution of 4-(pyridin-4-yl)naphth-1-ylamine (D3; 176mg, 0.80 mmole) and triethylamine (0.12ml, 0.88 mmole) in dichloromethane (20ml) over 0.5h. at room temperature, whilst passing a slow stream of argon through the reaction mixture. The mixture was stirred for a further 15 min. at room temperature before addition of a solution of 3-(2-dimethylaminoethoxy)-4-iodoaniline (200mg, 0.65 mmole, D50 in WO 95/15954) in dichloromethane over 5 min. After stirring overnight the reaction mixture was washed with 10% aqueous sodium carbonate, the organic layer dried (Na_2SO_4) and concentrated *in vacuo* to a yellow oil. Purification by flash chromatography eluting with 10% methanol/dichloromethane and trituration with diethyl ether afforded the title compound as a white crystalline solid (160mg, 45%).

^1H NMR (250MHz, d^6DMSO) δ (ppm): 9.51 (s, 1H), 9.19 (s, 1H), 8.90 (d, 2H), 8.43 (d, 1H), 8.32 (d, 1H), 8.04 (d, 1H), 7.82 (m, 3H), 7.70 (m, 3H), 7.55 (s, 1H), 7.07 (d, 1H), 4.29 (t, 2H), 2.92 (t, 2H), 2.69 (s, 6H).

MS: m/z = 553 (MH^+)

Example 10**N-[2,3-Dichlorophenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea**

The title compound was prepared from 2,3-dichlorophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: m/z = 493/495 (MH^+).

Example 11**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[naphth-1-yl]urea**

The title compound was prepared from naphth-1-yl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to

5 Example 1.

MS: $m/z = 476$ (MH^+)

Example 12**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[2-nitrophenyl]urea**

10 The title compound was prepared from 2-nitrophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 471$ (MH^+)

15 Example 13**N-[3-Chloro-4-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea**

The title compound was prepared from 3-chloro-4-methylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

20 MS: $m/z = 474$ (MH^+)

Example 14**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[3-methylthiophenyl]urea**

The title compound was prepared from 3-methylthiophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

25 MS: $m/z = 472$ (MH^+)

Example 15**30 N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[4-methylthiophenyl]urea**

The title compound was prepared from 4-methylthiophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 472$ (MH^+)

Example 16

N-[3-Chloro-2-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

- 5 The title compound was prepared from 3-chloro-2-methylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 474$ (MH^+)

10 **Example 17**

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[3-methyl-4-(pyridin-4-yl)phenyl]urea

- The title compound was prepared from 3-methyl-4-(pyridin-4-yl)phenyl isocyanate (D5) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar
15 procedure to Example 1.

MS: $m/z = 517$ (MH^+)

Example 18

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[2-fluoro-5-nitrophenyl]urea

- 20 The title compound was prepared from 2-fluoro-5-nitrophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 489$ (MH^+)

25 **Example 19**

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[phenyl]urea

- The title compound was prepared from phenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to
Example 1.

- 30 MS: $m/z = 426$ (MH^+)

Example 20

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[2,3-dimethylphenyl]urea

The title compound was prepared from 2,3-dimethylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 454$ (MH^+)

5

Example 21

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[3-ethylphenyl]urea

The title compound was prepared from 3-ethylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to

10 Example 1.

MS: $m/z = 454$ (MH^+)

Example 22

N-[3-n-Butoxyphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

15 The title compound was prepared from 3-n-butoxyphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 498$ (MH^+)

20

Example 23

N-[2,5-Dichlorophenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

The title compound was prepared from 2,5-dichlorophenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

25 MS: $m/z = 494$ (MH^+)

Example 24

N-[4-Chloro-2-trifluoromethylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

30 The title compound was prepared from 4-chloro-2-trifluoromethylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 1.

MS: $m/z = 528$ (MH^+)

Example 25**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-4-bromonaphth-1-ylacetamide**

The title compound was prepared from 4 bromonaphth-1-ylacetic acid (J.Org.Chem., 1951, 16, 1588) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) following a similar procedure to Example 3 (46%).

¹H NMR (250 MHz, CDCl₃) δ (ppm) : 10.48 (s, 1H), 8.21-8.12 (m, 2H), 7.87 (d, 1H), 7.75-7.60 (m, 3H), 7.37-7.45 (m, 2H), 7.00 (d, 1H), 4.15 (s, 2H), 4.00 (m, 2H), 2.7 (m, 2H), 2.30 (s, 6H).

Example 26**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-4-bromo-3-methylphenylacetamide**

The title compound was prepared from 4 bromo-3-methylphenylacetic acid (D8) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) following a similar procedure to Example 3.

¹H NMR (250 MHz, CDCl₃) δ(ppm) : 7.61 (s, 1H), 7.50 (d, 1H), 7.42 (d, 1H), 7.23 (s, 1H), 7.10 (s, 1H), 6.91 (d, 1H), 6.65 (d, 1H), 4.1-3.96 (m, 2H), 3.55 (s, 2H), 2.88-2.75 (m, 2H), 2.40 (s, 6H), 2.28 (s, 3H).

Example 27**N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide**

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylacetic acid (D9) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) following a similar procedure to Example 3

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.75 (dd, 2H), 8.1 (d, 1H), 7.9 (d, 1H), 7.65-7.35 (m, 9H), 6.5 (dd, 1H), 4.2 (s, 2H), 4.08 (t, 2H), 2.8 (t, 2H), 2.37 (s, 6H).

Example 28**N-[4-n-Butyl-3-(dimethylaminoethoxy)phenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide**

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylacetic acid (D9) and 4-butyl-3-(2-dimethylaminoethoxy)aniline (D14) following a similar procedure to Example 3 to give the title compound as needles from ether mp 92 - 94°C (62%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.75 (d, 2H), 8.12 (d, 1H), 7.9 (d, 1H), 7.65 - 7.4 (m, 6H), 7.2 (d, 1H), 7.15 (s, 1H), 6.95 (d, 1H), 6.6 (dd, 1H), 4.2 (s, 2H), 4.0 (t, 2H), 2.7 (t, 2H), 2.5 (t, 2H), 2.3 (s, 6H), 1.45 (quintet, 2H), 1.3 (sextet, 2H), 0.85 (t, 3H).

5 **Example 29**

N-[4-n-Butyl-3-(2-dimethylaminoethoxy)phenyl]-2,3-dichlorophenylacetamide

The title compound was prepared from 4-butyl-3-(2-dimethylaminoethoxy)aniline (D14) and 2,3-dichlorophenylacetic acid (D17) following a similar procedure to Example 3 to give the title compound as crystals from ether/petrol mp 106 - 108°C (49%).

10 ¹H NMR (250MHz, CDCl₃) δ (ppm): 7.45 (dd, 1H), 7.35 - 7.2 (m, 4H), 7.0 (d, 1H), 6.75 (dd, 1H), 4.05 (t, 2H), 3.85 (s, 2H), 2.75 (t, 2H), 2.55 (t, 2H), 2.35 (s, 6H), 1.5 (quintet, 2H), 1.35 (sextet, 2H), 0.90 (t, 3H).

Example 30

15 **N-[2,3-Dichlorophenyl]-N'-[3-(3-dimethylaminopropyl)-4-iodophenyl]urea**

The title compound was prepared from 2,3-dichlorophenyl isocyanate and 3-(3-dimethylaminopropyl)-4-iodoaniline (D21) using a similar procedure to Example 1.

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.20-8.11 (m, 2H), 7.73-7.26 (m, 2H), 7.30-7.10 (m, 4H), 2.75-2.58 (m, 4H), 2.50 (s, 6H), 2.00-1.83 (m, 2H).

20

Example 31

N-[3-(3-Dimethylaminopropyl)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 3-(3-dimethylaminopropyl)-4-iodoaniline (D21) using a similar procedure to Example 9.

25 ¹H NMR (250MHz, CDCl₃) δ (ppm): 8.68 (d, 2H), 8.47 (s, 1H), 8.22 (s, 1H), 8.05 (d, 1H), 7.83-7.71 (m, 2H), 7.50 (d, 1H), 7.40-7.20 (m, 6H), 6.97 (dd, 1H), 2.54 (t, 2H), 2.40 (t, 2H), 2.28 (s, 6H), 1.80-1.63 (m, 2H).

Example 32

30 **N-[3-(3-Dimethylaminopropyl)-4-iodophenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide**

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylacetic acid (D9) and 3-(3-dimethylaminopropyl)-4-iodoaniline (D21) using a similar procedure to Example 3

¹H NMR (250MHz,CDCl₃) δ (ppm): 8.75 (d, 2H), 8.10 (d, 1H), 7.90 (d, 1H), 7.68-7.25 (m, 9H), 7.00 (dd, 1H), 4.22 (s, 2H), 2.70-2.60 (m, 2H), 2.35-2.20 (m, 2H), 2.22 (s, 6H), 1.80-1.62 (m, 2H).

5 **Example 33**

N-[3-(3-Dimethylaminopropoxy)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 3-(3-dimethylaminopropoxy)-4-iodoaniline (D26) using a similar procedure to Example 9 as a pale yellow oil (36%). This material was converted to its hydrochloride salt as a yellow solid from acetone.

¹H NMR (free base) (250 MHz, CDCl₃) δ (ppm): 8.70 - 8.65 (m, 2H), 8.16 (s, 1H), 8.04 (s, 1H), 7.98 (d, 1H), 7.80 - 7.70 (m, 2H), 7.45 - 7.25 (m, 6H), 7.12 (d, 1H), 6.42 (dd, 1H), 3.80 (t, 2H), 2.45 (t, 2H), 2.23 (s, 6H), 1.85 (quintet, 2H).

15 **Example 34**

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[5-(pyridin-4-yl)naphth-1-yl]urea

The title compound was prepared from 5-(pyridin-4-yl)naphth-1-ylamine (D22) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 9 as a yellow oil (29%). This material was converted to its hydrochloride salt as a yellow solid from acetone.

¹H NMR (free base) (250 MHz, CDCl₃) δ (ppm): 8.74 - 8.69 (m, 2H), 8.01 (d, 1H), 7.90 - 7.70 (m, 2H), 7.68 - 7.58 (m, 2H), 7.48 - 7.30 (m, 6H), 7.15 (s, 1H), 6.42 (m, 1H), 3.97 (br t, 2H), 2.73 (t, 2H), 2.34 (s, 6H).

25 **Example 35**

N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-5-(pyridin-4-yl)naphth-1-ylacetamide

The title compound was prepared from 5-(pyridin-4-yl)naphth-1-ylacetic acid (D24) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO95/15954) using a similar procedure to Example 3 as a yellow oil. This material was converted to its hydrochloride salt as a white solid from acetone.

¹H NMR (HCl salt) (250 MHz, CDCl₃) δ (ppm): 8.74 - 8.69 (m, 2H), 8.48 (s, 1H), 8.15 (d, 1H), 7.78 (d, 1H), 7.63 - 7.50 (m, 3H), 7.45 - 7.35 (m, 4H), 7.29 (d, 1H), 6.89 (dd, 1H), 4.26 (t, 2H), 4.22 (s, 2H), 3.18 (t, 2H), 2.70 (s, 6H).

Example 36**N-[4-Methoxy-5-((S)-1-methylpyrrolidin-2-ylmethoxy)phenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide**

5 4-(Pyridin-4-yl)naphth-1-ylacetic acid (D9, 0.33g, 1.25 mmole) and 4-methoxy-3-((S)-1-methylpyrrolidin-2-ylmethoxy)aniline (Description 2 in EP 95/01578) was suspended in dichloromethane (20ml). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.264g, 1.38 mmole) and 1-hydroxybenzotriazole hydrate (0.21g, 1.55 mmole) were added and the mixture stirred at room temperature for 48h. The mixture was washed with
10 20% aqueous potassium carbonate and the organic phase dried (Na₂SO₄), filtered and concentrated *in vacuo* gave a gum (0.51g), which was purified by silica chromatography using methanol: dichloromethane mixture as elutant. Evaporation of the eluate *in vacuo* gave a white solid (0.074g, 15%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.70 (d, 2H), 8.10 (d, 1H), 7.85 (d, 1H), 7.58 - 7.41
15 (m, 6H), 7.18 (d, 1H), 7.17 (m, 1H), 6.73 (d, 1H), 4.05 (s, 2H), 3.99 - 3.84 (m, 3H), 3.76 (s, 3H), 3.11 (m, 1H), 2.72 (m, 1H), 2.37 (s, 3H), 2.30 - 1.38 (br m, 5H).

Example 37**1-(2,3-Dichlorophenylaminocarbonyl)-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1H-indole**

20 The title compound was prepared from 2,3-dichlorophenyl isocyanate and 2,3-dihydro-6-(2-dimethylaminethoxy)-5-iodo-1H-indole (D31) using a similar procedure to Example 1 as a pale yellow oil (17%). This material was converted to its hydrochloride salt as a white solid from acetone.

25 ¹H NMR (free base) (250 MHz, CDCl₃) δ (ppm): 8.26-8.20 (m, 1H), 7.69 (s, 1H), 7.51 (s, 1H), 7.30 - 7.16 (m, 3H), 4.23 (t, 2H), 4.17 (t, 2H), 3.21 (t, 2H), 2.96 (t, 2H), 2.51 (s, 6H).

Example 38**2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole**

30 The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 2,3-dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1H-indole (D31) using a similar procedure to

Example 9 as a pale yellow oil (33%). This material was converted to its hydrochloride salt as a yellow solid from acetone.

¹H NMR (free base) (250 MHz, CDCl₃) δ (ppm): 8.74 - 8.69 (m, 2H), 8.00 (d, 1H), 7.89 - 7.80 (m, 2H), 7.70 (s, 1H), 7.63 - 7.38 (m, 6H), 7.01 (s, 1H), 4.25 (t, 2H), 4.08 (t, 2H),
5 3.21 (t, 2H), 2.78 (t, 2H), 2.35 (s, 6H).

Example 39

5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

10 The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 5-bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D34) using a similar procedure to Example 9.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.73 (d, 2H), 8.00 (d, 1H), 7.85 - 7.90 (m, 2H), 7.81 (s, 1H), 7.42 - 7.62 (m, 3H), 7.42 (d, 2H), 7.33 (s, 1H), 6.89 (s, 1H), 4.31 (t, 2H),
15 4.17 (t, 2H), 3.28 (t, 2H), 2.87 (t, 2H), 2.43 (s, 6H).

Example 40

5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole

20 The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 5-bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D34) using a similar procedure to Example 9.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.66 (d, 2H), 7.76 (s, 1H), 7.69 (d, 1H), 7.44 (dd, 1H), 7.38 (d, 2H), 7.27 - 7.31 (m, 2H), 6.64 (s, 1H), 4.08 - 4.18 (m, 4H), 3.20 (t, 2H),
25 2.80 (t, 2H), 2.37 (s, 6H).

Example 41

5-Chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

30 The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D36) using a similar procedure to Example 9.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.73 (d, 2H), 8.00 (dd, 1H), 7.82 - 7.90 (m, 3H), 7.41 - 7.47 (m, 5H), 7.16 (s, 1H), 6.90 (s, 1H), 4.29 (t, 2H), 4.11 (t, 2H), 3.26 (t, 2H), 2.75 (t, 2H), 2.32 (s, 6H).

5 **Example 42**

5-Chloro-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D36) using a similar
10 procedure to Example 9.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.66 (d, 2H), 7.79 (s, 1H), 7.68 (d, 1H), 7.45 (dd, 1H), 7.38 (d, 2H), 7.29 (d, 1H), 7.14 (s, 1H), 6.62 (s, 1H), 4.08 - 4.18 (m, 4H), 3.20 (t, 2H), 2.79 (t, 2H), 2.36 (s, 6H)

15 **Example 43**

2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1-(4-(pyridin-4-yl)naphth-1-ylaminocarbonyl)-1H-indole

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole (D39) using a similar procedure
20 to Example 9.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.73 (d, 2H), 8.00 (d, 1H), 7.87 - 7.92 (m, 2H), 7.69 (s, 1H), 7.41 - 7.61 (m, 5H), 6.99 (s, 1H), 6.85 (s, 1H), 4.27 (t, 2H), 4.08 (t, 2H), 3.26 (t, 2H), 2.74 (t, 2H), 2.61 (q, 2H), 2.32 (s, 6H), 1.18 (t, 3H).

25 **Example 44**

1-[3-Chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole (D39) using a similar procedure
30 to Example 9.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.66 (d, 2H), 7.69 (d, 1H), 7.63 (s, 1H), 7.46 (dd, 1H), 7.38 (d, 2H), 7.28 (d, 1H), 6.96 (s, 1H), 6.59 (s, 1H), 4.07 - 4.17 (m, 4H), 3.19 (t, 2H), 2.81 (t, 2H), 2.60 (q, 2H), 2.39 (s, 6H), 1.17 (t, 3H).

Example 45**2,3-Dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole**

5 The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylacetic acid (D9) and 2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D40) using a similar procedure to Example 3 as a pale yellow oil (57%).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.75 - 8.71 (m, 2H), 8.01 (d, 1H), 7.97 (d, 1H), 7.88 (d, 1H), 7.62 - 7.35 (m, 6H), 7.07 (d, 1H), 6.65 (dd, 1H), 4.27 (s, 2H), 4.26 (t, 2H),
10 4.01 (t, 2H), 3.19 (t, 2H), 2.66 (t, 2H), 2.28 (s, 6H)

Example 46**5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole**

15 The title compound was prepared from 2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole (E45) and benzyltrimethylammonium tribromide using a similar procedure to Description 29 (65%). This material was converted to its hydrochloride salt as a white solid from acetone.

¹H NMR (free base) (250 MHz, CDCl₃) δ (ppm): 8.75 - 8.70 (m, 2H), 8.02 - 7.91 (m, 2H), 7.87 (d, 1H), 7.63 - 7.36 (m, 6H), 7.33 (s, 1H), 4.27 (t + s, 4H), 4.08 (t, 2H), 3.20 (t, 2H), 2.75 (t, 2H), 2.33 (s, 6H).

Example 47**2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole**

25 The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylacetic acid (D9) and 2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole (D39) using a similar procedure to Example 3 as a yellow oil (82%). This material was converted to its hydrochloride salt as a yellow solid from acetone.

30 ¹H NMR (free base) (250 MHz, CDCl₃) δ (ppm): 8.75 - 8.70 (m, 2H), 8.00 (d, 1H), 7.94 (s, 1H), 7.87 (d, 1H), 7.50 - 7.35 (m, 6H), 6.98 (s, 1H), 4.26 (s, 2H), 4.24 (t, 2H), 4.04 (t, 2H), 3.18 (t, 2H), 2.71 (t, 2H), 2.60 (q, 2H), 2.30 (s, 6H), 1.16 (t, 3H).

Example 48**N-[4-Bromo-3-(2-dimethylaminoethoxy)phenyl]-2,3-dihydro-4-(pyridin-4-yl)naphth-1-ylacetamide**

- 4-Bromo-3-(2-dimethylaminoethoxy)aniline (D46), (258mg, 1 mmole) in
5 dichloromethane (10ml) was treated with 4-(pyridin-4-yl)naphth-1-ylacetyl chloride
(from D9) (282mg, 1 mmole) and triethylamine (1 mmole, 100mg), then stirred at room
temperature for 4h. The reaction was washed with saturated aqueous potassium carbonate
solution, dried (Na₂SO₄), and chromatographed on silica in a gradient of 5-20% methanol
in CH₂Cl₂ to give the title compound 330mg, (65%).
10 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.75 (d, 2H), 8.1 (d, 1H), 7.9 (d, 1H), 7.65 - 7.25
(m, 9H), 6.5 (dd, 1H), 4.2 (s, 2H), 4.05 (t, 2H), 2.8 (t, 2H), 2.35 (s, 6H).

Example 49**N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-iodo-3-(1-methylpiperidin-4-
15 yloxy)phenyl]urea**

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 4-iodo-
3-(1-methylpiperidin-4-yloxy)aniline (D41) using a similar procedure to Example 9
(67%)

- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.6 (d, 2H), 8.5 (s, 1H), 8.35 (s, 1H), 7.5 (m, 2H),
20 7.45 - 7.25 (m, 4H), 7.15 (d, 1H), 6.45 (dd, 1H), 4.4 (m, 1H), 2.7 (m, 2H), 2.4 (m, 2H) 2.3
(s, 3H), 1.9 (m, 4H).

Example 50**N-[4-Chloro-3-(1-methylpiperidin-4-yloxy)phenyl]-N'-[3-chloro-4-(pyridin-4-
25 yl)phenyl]urea**

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 4-
chloro-3-(1-methylpiperidin-4-yloxy)aniline (D43) as described in Example 49 in 27%
yield.

- ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (d, 2H), 8.45 (s, 1H), 8.3 (s, 1H), 7.6 (s, 1H),
30 7.4 - 7.0 (m, 5H), 6.6 (d, 1H), 6.25 (m, 1H), 4.35 (m, 1H), 2.65 (m, 2H), 2.4 (m, 2H), 2.25
(s, 3H), 1.9 (m, 4H).

Example 51**5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(1-methylpiperidin-4-yloxy)-1H-indole**

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 5-bromo-2,3-dihydro-6-(1-methylpiperidin-4-yloxy)-1H-indole (D52) as described in Example 49 in 64% yield.

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.7 (m, 2H), 7.8 (s, 1H), 7.7 (s, 1H), 7.5 - 7.25 (m, 5H), 6.65 (s, 1H), 4.5 (m, 1H), 4.15 (t, 2H), 3.2 (t, 2H), 2.7 (m, 2H), 2.35 (m, 2H), 2.3 (s, 3H), 2.0 (m, 4H).

Example 52**N-[4-Chloro-3-(1-methylpiperidin-4-yloxy)phenyl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]urea**

The title compound was prepared from 4-(pyridin-4-yl)-3-trifluoromethylaniline (D54) and 4-chloro-3-(1-methylpiperidin-4-yloxy)aniline (D43) as described in Example 49 in 81% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (d, 2H), 7.85 (s, 1H), 7.7 (m, 2H), 7.6 (s, 1H), 7.13 - 7.15 (m, 5H), 6.65 (dd, 1H), 4.4 (m, 1H), 2.7 (m, 2H), 2.35 (m, 2H), 2.3 (s, 3H), 2.0 (m, 4H).

Example 53**N-[4-Chloro-3-(2-dimethylaminoethoxy)phenyl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]urea**

The title compound was prepared from 4-(pyridin-4-yl)-3-trifluoromethylaniline (D54) and 4-chloro-3-(2-dimethylaminoethoxy)aniline (D56) as described in Example 49 in 44% yield.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (d, 2H), 8.25 (s, 1H), 8.0 (s, 1H), 7.7 (s, 1H), 7.85 (d, 1H), 7.35 (s, 1H), 7.25 (m, 3H), 7.2 (d, 1H), 6.65 (dd, 1H), 4.1 (t, 2H), 2.8 (t, 2H), 2.35 (s, 6H).

Example 54**5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole**

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 5-bromo-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole (D58) following a similar procedure to Example 9 to give the title compound as buff needles, 51%. (m.p. 195-197°C).

- 5 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (d, 2H), 7.75-7.65 (m, 2H), 7.5-7.40 (m, 3H), 7.35-7.25 (m, 2H), 6.7 (s, 1H), 4.1 (t, 2H), 3.95-3.8 (m, 2H), 3.2 (t, 2H), 3.0 (br d, 1H), 2.75 (br d, 1H), 2.3 (s, 3H), 2.0-1.55 (m, 6H), 1.2-1.0 (m, 1H).

Example 55

- 10 **5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole**

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 5-bromo-2,3-dihydro-6-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole (D60) following a similar procedure to Example 9 to give the title compound as colourless needles 35%,
15 (m.p. 210-213°C).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (d, 2H), 7.75 (s, 1H), 7.65 (s, 1H), 7.45 (dd, 1H), 7.4 (m, 2H), 7.3 (m, 2H), 6.6 (s, 1H), 4.1 (t, 2H), 4.0 (d, 2H), 3.2 (t, 2H), 3.1 (t, 1H), 2.8-2.7 (m, 1H), 2.55 (s, 3H), 2.4-2.25 (m, 2H), 2.1-1.9 (m, 1H), 1.9-1.65 (m, 2H).

20 Example 56

5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)oxy]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

- The title compound was prepared from 4-(4-pyridyl)-1-naphthylamine (D3) and (5-bromo-6-[(1-methyl-4-piperidinyl)oxy]indoline (D52) following a similar procedure to
25 Example 9 to give the title compound as a yellow solid (55%) (m.p. 119-123°C).

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.75 (d, 2H), 8.0 (d, 2H), 7.9-7.8 (m, 2H), 7.65-7.4 (m, 5H), 7.35 (s, 1H), 6.8 (s, 1H), 4.45 (m, 1H), 4.3 (t, 2H), 3.3 (t, 2H), 2.65 (m, 2H), 2.35 (m, 2H), 2.25 (s, 3H), 1.9 (m, 4H).

30 Example 57

5-Bromo-1-[3-chloro-4-(4-pyridyl)phenylaminocarbonyl]-6-[(1-methylpiperidin-3-yl)oxy]indoline

The title compound was prepared from 3-chloro-4-(pyridin-4-yl)aniline (D23) and 5-bromo-2,3-dihydro-6-[(1-methylpiperidin-3-yl)oxy]-1H-indole (D61) following a similar procedure to Example 9 to give the title compound as needles from ether (m.p. 114-117°C) in 57% yield.

- 5 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (s, 2H), 7.8 (s, 1H), 7.65 (s, 1H), 7.45 (d, 1H), 7.4 (d, 2H), 7.3 (d, 2H), 6.65 (s, 1H), 4.4 (m, 1H), 4.1 (t, 2H), 3.2 (t, 2H), 3.0 (m, 1H), 2.6 (m, 1H), 2.3 (s, 3H), 2.15-1.95 (m, 3H), 1.35 (m, 1H), 1.7-1.45 (m, 2H).

Example 58

- 10 **5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole**

The title compound was prepared from 5-bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole (D63) and 3-chloro-4-(pyridin-4-yl)aniline (D23) following a similar procedure to Example 9 to give the title compound as needles from ether (m.p. 236-240°C).

- 15 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (d, 2H), 7.7 (m, 2H), 7.45 (dd, 1H), 7.4 (d, 2H), 7.3 (m, 2H), 6.85 (s, 1H), 4.1 (t, 2H), 3.85 (d, 2H), 3.15 (t, 2H), 2.9 (m, 2H), 2.3 (t, 3H), 2.15-1.8 (m, 5H), 1.4 (m, 2H).

20 Example 59

5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[5-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

The title compound was prepared from 5-(pyridin-4-yl)naphth-1-yl isocyanate (D65) and 5-bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole (D34) using a similar procedure to Example 1.

- 25 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.73 (d, 2H), 8.03 (d, 1H), 7.78 (s, 1H), 7.75-7.70 (m, 2H), 7.60 (t, 1H), 7.47 (t, 1H), 7.45-7.40 (m, 3H), 7.31 (s, 1H), 6.85 (s, 1H), 4.26 (t, 2H), 4.09 (t, 2H), 3.24 (t, 2H), 2.76 (t, 2H), 2.33 (s, 6H).

30 Example 60

N-[4-Acetylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

The title compound was prepared from 4-acetylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (Description 50 in WO 95/15954) using a similar procedure to Example 1 as a white crystalline solid (24%).

¹H NMR (250MHz, d⁶DMSO) δ(ppm): 9.00 (s, 1H), 8.90 (s, 1H), 7.74 (d, 2H), 7.46 (d, 1H), 7.42 (d, 2H), 7.14 (d, 1H), 6.66 (dd, 1H), 3.92 (t, 2H), 2.55 (t, 2H), 2.35 (s, 3H), 2.12 (s, 6H).

Example 61

N-[3-Acetylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea

The title compound was prepared from 3-acetylphenyl isocyanate and 3-(2-dimethylaminoethoxy)-4-iodoaniline (Description 50 in WO 95/15954) using a similar method to Example 1 (66%).

¹H NMR (250MHz, d⁶DMSO) δ(ppm): 9.01 (s, 1H), 8.93 (s, 1H), 8.10 (d, 1H), 7.67 (m, 3H), 7.48 (t, 1H), 7.35 (d, 1H), 6.86 (dd, 1H), 4.12 (t, 2H), 2.76 (t, 2H), 2.61 (s, 3H), 2.33 (s, 6H).

Example 62

2,3-Dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole (D68) using a similar procedure to Example 9 as a white solid (27%).

¹H NMR (250MHz, CDCl₃) δ(ppm): 8.73 (d, 2H), 7.89 (m, 4H), 7.52 (m, 3H), 7.42 (d, 2H), 7.14 (d, 1H), 6.93 (s, 1H), 6.84 (d, 1H), 4.27 (t, 2H), 3.29 (t, 2H), 2.62 (t, 2H), 2.29 (t, 2H), 2.21 (s, 6H), 1.80 (m, 2H).

Example 63

5-Bromo-2,3-dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

To a solution of 6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole (E62, 50mg, 0.11mmole) in dichloromethane (2ml) at 0°C was added benzyltrimethylammonium tribromide (43mg, 0.11mmole) and the mixture left at 0°C for 72h, then further benzyltrimethylammonium tribromide (43mg,

0.11mmole) was added and the mixture stirred at 0°C for 1 h. The mixture was washed with aqueous 10% sodium carbonate, the organics dried (Na₂SO₄), evaporated *in vacuo* and triturated with diethyl ether to give the title compound as a pale yellow solid (23mg, 39%).

- 5 ¹H NMR (250MHz,CDCl₃) δ(ppm): 8.73 (d, 2H), 7.94 (m, 4H), 7.54 (m, 3H), 7.42 (d, 2H), 7.36 (s, 1H), 6.87 (s, 1H), 4.28 (t, 2H), 3.30 (t, 2H), 2.72 (t, 2H), 2.38 (t, 2H), 2.25 (s, 6H), 1.81 (m, 2H).

Example 64

- 10 **5-Chloro-2,3-dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole**

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D1) and 5-chloro-2,3-dihydro-6-(3-dimethylaminopropyl)-1H-indole (D70) using a similar procedure to Example 9 as a white solid (38%)

- 15 ¹H NMR (250MHz,CDCl₃) δ(ppm): 8.74 (dd, 2H), 7.99 (d, 1H), 7.90 (m, 3H), 7.51 (m, 3H), 7.43 (dd, 2H), 7.19 (s, 1H), 6.89 (s, 1H), 4.30 (t, 2H), 3.31 (t, 2H), 2.73 (t, 2H), 2.50 (t, 2H), 2.35 (s, 6H), 1.88 (m, 2H).

Example 65

- 20 **2,3-Dihydro-6-(3-dimethylaminopropyl)-5-iodo-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole**

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D1) and 2,3-dihydro-5-iodo-6-(3-dimethylaminopropyl)-1H-indole (D71) using a similar procedure to Example 9 as a white solid (38%)

- 25 ¹H NMR (250MHz,CDCl₃) δ(ppm): 8.73 (dd, 2H), 7.99 (d, 1H), 7.91 (m, 3H), 7.50 (m, 3H), 7.43 (dd, 2H), 6.94 (s, 1H), 4.28 (t, 2H), 3.29 (t, 2H), 2.72 (t, 2H), 2.50 (t, 2H), 2.35 (s, 6H), 1.84 (m, 2H). NH not observed.

Example 66

- 30 **N-[2,3-Dichloro-4-(pyridin-4-yl)phenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea**

The title compound was prepared from 2,3-dichloro-4-(pyridin-4-yl)aniline (D72) and 3-(2-dimethylaminoethoxy)-4-iodoaniline (D50 in WO 95/15954) using a similar procedure to Example 9 as a gum (27%).

¹H NMR (250 MHz, d⁶DMSO) δ (ppm): 9.7 (s, 1H), 8.65 (m, 3H), 8.3 (d, 1H), 7.7 (d, 1H), 7.5 (d, 2H), 7.4 (d, 1H), 7.35 (s, 1H), 6.85 (d, 1H), 4.1 (t, 2H), 2.7 (t, 2H), 2.25 (s, 6H).

Example 67

5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 5-bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1H-indole (D83) using a similar procedure to Example 9 as a white solid (52%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.72 (d, 2H), 7.98 (d, 1H), 7.92 - 7.84 (m, 3H), 7.62 - 7.40 (m, 5H), 7.36 (s, 1H), 6.97 (s, 1H), 4.26 (t, 2H), 3.26 (t, 2H), 2.78 (br d, 2H), 2.63 (d, 2H), 2.21 (s, 3H), 1.83 (td, 2H), 1.70 - 1.50 (t, 3H), 1.50 - 1.25 (m, 2H).

Example 68

5-Bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole

The title compound was prepared from 4-(pyridin-4-yl)naphth-1-ylamine (D3) and 5-bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1H-indole (D92), using a similar procedure to Example 9, as a pale brown solid (50%).

¹H NMR (250MHz, CDCl₃) δ (ppm): 8.72 (d, 2H), 7.98 (d, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.86 (d, 1H), 7.61 - 7.40 (m, 5H), 7.33 (s, 1H), 6.93 (s, 1H), 4.25 (t, 2H), 3.26 (t, 2H), 2.85 - 2.56 (m, 3H), 2.28 (s, 3H), 2.12 - 1.92 (m, 2H), 1.83 - 1.33 (m, 8H).

Pharmacological Data

5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} Receptor Binding

HEK 293 cells expressing 5-HT_{1A} receptors (4 x 10⁷/ml) were homogenised in Tris buffer and stored in 1ml aliquots. CHO cells expressing 5-HT_{1B} receptors (4 x 10⁷

cells/ml) were homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT_{1D} receptors (0.563×10^8 /ml) were homogenised in Tris buffer and stored in 1 ml aliquots.

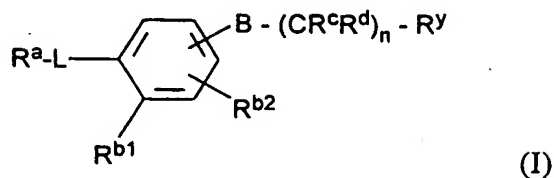
- 0.4 ml of a cell suspension was incubated with [³H]-5-HT (4nM) for 5-HT_{1B/1D} receptors and [³H]-8-OH DPAT (1nM) for 5-HT_{1A} receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug was tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume was 0.5 ml. Incubation was stopped by rapid filtration using a Packard Filtermate (filters pre-soaked in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values were calculated from the IC₅₀ generated by an iterative least squares curve fitting programme.

Examples 8, 9, 10, 27, 34, 35, 38, 39, 46, 49, 50, 51, 56, 59, 60, 66 and 67 had pKi values >8.0 at 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors.

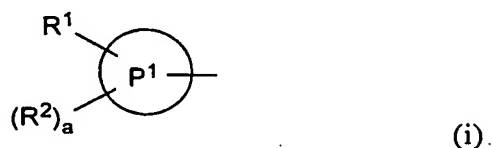
15

CLAIMS

1. A compound of formula (I) or a salt thereof:



in which R^a is a group of formula (i)



10

in which P^1 is phenyl, bicyclic aryl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;

R^1 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, COC_{1-6} alkyl, C_{1-6} alkoxy,

15 hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{1-6} alkanoyl, nitro, trifluoromethyl, cyano, SR^9 , SOR^9 , SO_2R^9 , $SO_2NR^{10}R^{11}$, CO_2R^{10} , $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_cCO_2R^{11}$, $(CH_2)_cNR^{10}R^{11}$, $(CH_2)_cCONR^{10}R^{11}$, $(CH_2)_cNR^{10}COR^{11}$, $(CH_2)_cCO_2C_{1-6}$ alkyl, $CO_2(CH_2)_cOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where

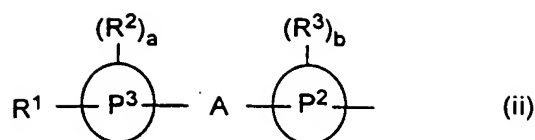
20 R^9 , R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl and c is 1 to 4;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl,

C_{3-6} cycloalkenyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10} , $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1 ;

25 a is 1, 2 or 3;

or R^a is a group of formula (ii)



wherein P² and P³ are independently phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a bond or oxygen, S(O)_m where m is 0 to 2, carbonyl, or CH₂ or NR⁴ where R⁴ is hydrogen or C₁₋₆alkyl;

R¹ is as defined above for formula (i) or R¹ is a 5 to 7-membered heterocyclic ring, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by C₁₋₆ alkyl, halogen or C₁₋₆ alkanoyl;

R² and R³ are independently hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkenyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO₂R¹⁰, CONR¹⁰R¹¹, NR¹⁰R¹¹ where R¹⁰ and R¹¹ are as defined for R¹;

and a and b are independently 1, 2 or 3;

L is a group of formula

- Y - C (=V) - DG -

in which Y is - NH -, NR⁵ where R⁵ is C₁₋₆alkyl, or Y is - CH₂ - or - O - ; V is oxygen or sulphur;

D is nitrogen, carbon or a CH group, G is hydrogen or C₁₋₆alkyl providing that D is nitrogen or a CH group, or G together with R^{b1} forms a group W where W is (CR¹⁶R¹⁷)_t where t is 2, 3 or 4 and R¹⁶ and R¹⁷ are independently hydrogen or C₁₋₆alkyl or W is (CR¹⁶R¹⁷)_u-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, CR¹⁶=CR¹⁷, CR¹⁶=N, =CR¹⁶O, =CR¹⁶S or =CR¹⁶-NR¹⁷;

B is CH₂, oxygen, S(O)_p where p is 0, 1 or 2, NR⁶ where R⁶ is hydrogen or C₁₋₆alkyl or B is CR⁷=CR⁸ where R⁷ and R⁸ are independently hydrogen or C₁₋₆alkyl;

R^c and R^d are independently hydrogen or C₁₋₆alkyl;

R^Y is a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or R^Y is a group of formula -NR^eR^f in which

R^e and R^f are independently hydrogen, C₁₋₆alkyl or aralkyl;

- 5 R^{b1} and R^{b2} are independently hydrogen, halogen, hydroxy, C₁₋₆alkyl, trifluoromethyl, C₁₋₆alkoxy or aryl, or R^{b1} together with G forms a group W as defined above; and n is 0, 1, 2, 3 or 4.

2. A compound according to claim 1 in which R¹ is a halogen atom.

- 10 3. A compound according to claim 1 or 2 in which R² and/or R³ are each hydrogen, halogen or a C₁₋₆ alkyl group.

4. A compound according to any of the preceding claims in which P¹ and P² are phenyl or naphthyl.

15

5. A compound according to any of the preceding claims in which Y is -NH-.

6. A compound according to any of the preceding claims in which D is nitrogen and G is a hydrogen atom.

20

7. A compound according to any of the preceding claims in which R^{b1} and R^{b2} are hydrogen or halogen or R^{b1} together with G forms a -(CH₂)₂- group.

8. A compound according to any of the preceding claims in which B is oxygen.

25

9. A compound according to claim 1 which is

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-4-biphenyl]urea,

N-[4-bromo-3-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,

30 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]naphth-1-ylacetamide,

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromophenyl carbamate,

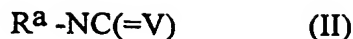
N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[(2-trifluoromethyl)phenyl]urea,

N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[(4-fluoro-3-nitro)phenyl]urea,

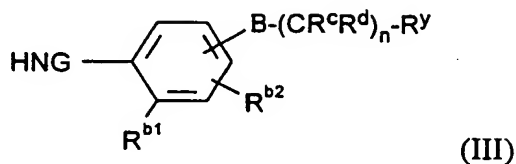
- N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[4-phenoxyphenyl]urea,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromophenylacetamide,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea,
 N-[2,3-dichlorophenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
 5 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[naphth-1-yl]urea, N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2-nitrophenyl]urea, N-[3-chloro-4-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea, N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[3-methylthiophenyl]urea,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[4-methylthiophenyl]urea, N-[3-chloro-
 10 2-methylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[3-methyl-4-(pyridin-4-yl)phenyl]urea, N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2-fluoro-5-nitrophenyl]urea, N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[phenyl]urea,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-N'-[2,3-dimethylphenyl]urea, N-[3-(2-
 15 dimethylaminoethoxy)-4-iodophenyl]-N'-[3-ethylphenyl]urea,
 N-[3-n-butoxyphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
 N-[2,5-dichlorophenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
 N-[4-chloro-2-trifluoromethylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromonaphth-1-ylacetamide,
 20 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-bromo-3-methylphenylacetamide,
 N-[3-(2-dimethylaminoethoxy)-4-iodophenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
 N-[4-n-butyl-3-(dimethylaminoethoxy)phenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
 N-[4-n-butyl-3-(2-dimethylaminoethoxy)phenyl]-2,3-dichlorophenylacetamide,
 N-[2,3-dichlorophenyl]-N'-[3-(3-dimethylaminopropyl)-4-iodophenyl]urea,
 25 N-[3-(3-dimethylaminopropyl)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea,
 N-[3-(3-dimethylaminopropyl)-4-iodophenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
 N-[3-(3-Dimethylaminopropoxy)-4-iodophenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]urea,
 N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-N'-[5-(pyridin-4-yl)naphth-1-yl]urea,
 N-[3-(2-Dimethylaminoethoxy)-4-iodophenyl]-5-(pyridin-4-yl)naphth-1-ylacetamide,
 30 N-[4-Methoxy-5-((S)-1-methyl-2-pyrrolidinylmethoxy)phenyl]-4-(pyridin-4-yl)naphth-1-ylacetamide,
 1-(2,3-Dichlorophenylaminocarbonyl)-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1H-indole,

- 2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-iodo-1-[4-(pyridin-4-yl)naphth-1-ylamino-carbonyl]-1H-indole,
5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
5 5-Bromo-2,3-dihydro-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-6-(2-dimethylaminoethoxy)-1H-indole,
5-Chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
5-Chloro-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-
10 dimethylaminoethoxy)-1H-indole,
2,3-Dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
1-[3-Chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(2-dimethylaminoethoxy)-5-ethyl-1H-indole,
15 2,3-Dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole,
5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-indole,
2,3-Dihydro-6-(2-imethylaminoethoxy)-5-ethyl-1-[4-(pyridin-4-yl)naphth-1-ylacetyl]-1H-
20 indole,
N-[4-Bromo-3-(2-dimethylaminoethoxy)phenyl]-2,3-dihydro-4-(pyridin-4-yl)naphth-1-ylacetamide,
N-[3-Chloro-4-(pyridin-4-yl)phenyl]-N'-[4-iodo-3-(1-methylpiperidin-4-yloxy)phenyl]urea,
25 N-[4-Chloro-3-(1-methyl-4-piperidinyloxy)phenyl]-N'-[3-chloro-4-(pyridin-4-yl)phenyl]urea,
5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-(1-methylpiperidin-4-yloxy)-1H-indole,
N-[4-Chloro-3-(1-methylpiperidin-4-yloxy)phenyl]-N'-[4-(pyridin-4-yl)-3-
30 trifluoromethylphenyl]urea,
N-[4-Chloro-3-(2-dimethylaminoethoxy)phenyl]-N'-[4-(pyridin-4-yl)-3-trifluoromethylphenyl]urea,

- 5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-3-yl)methoxy]-1H-indole,
 5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpyrrolidin-2-yl)methoxy]-1H-indole,
- 5 5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)oxy]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
 5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-3-yl)oxy]-1H-indole,
 5-Bromo-1-[3-chloro-4-(pyridin-4-yl)phenylaminocarbonyl]-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methoxy]-1H-indole,
- 10 5-Bromo-2,3-dihydro-6-(2-dimethylaminoethoxy)-1-[5-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
 N-[4-Acetylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
 N-[3-Acetylphenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
- 15 2,3-Dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
 5-Bromo-2,3-dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
 5-Chloro-2,3-dihydro-6-(3-dimethylaminopropyl)-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
- 20 2,3-Dihydro-6-(3-dimethylaminopropyl)-5-iodo-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
 N-[2,3-Dichloro-4-(pyridin-4-yl)phenyl]-N'-[3-(2-dimethylaminoethoxy)-4-iodophenyl]urea,
- 25 5-Bromo-2,3-dihydro-6-[(1-methylpiperidin-4-yl)methyl]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole,
 5-Bromo-2,3-dihydro-6-[2-(1-methylpiperidin-2-yl)ethyl]-1-[4-(pyridin-4-yl)naphth-1-ylaminocarbonyl]-1H-indole
- or pharmaceutically acceptable salts thereof.
- 30 10. A process for the preparation of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof which comprises:
- (a) where D is nitrogen and Y is NH, coupling a compound of formula (II):



in which R^a and V are as defined in formula (I) or a protected derivative thereof with a compound of formula (III).



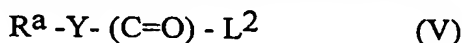
in which R^{b1} , R^{b2} , R^c , R^d , R^y , B , G and n are as defined in formula (I), or a protected derivative thereof; or

(b) where D is nitrogen and Y is NH or NR^5 , reacting a compound of formula (IV)



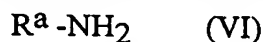
in which R^a and R^5 are as defined in formula (I) with a compound of formula (III) together with an appropriate urea forming agent;

(c) where D is nitrogen, reacting a compound of formula (V)

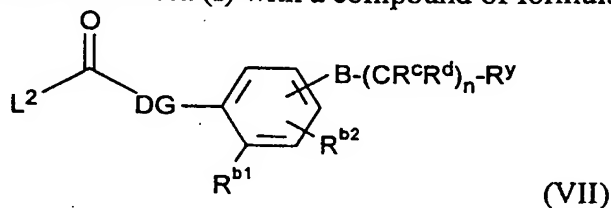


15 in which R^a is as defined in formula (I),
 Y is $-CH_2-$ or $-O-$ and L^2 is an appropriate leaving group, with a compound of formula (III)

(d) where D is carbon or CH , reacting a compound of formula (VI)



20 in which R^a is as defined in formula (I) with a compound of formula (VII)



in which D is carbon or CH , R^{b1} , R^{b2} , R^c , R^d , R^y , B , G and n are as defined in formula (I) and L^2 is an appropriate leaving atom and optionally thereafter:

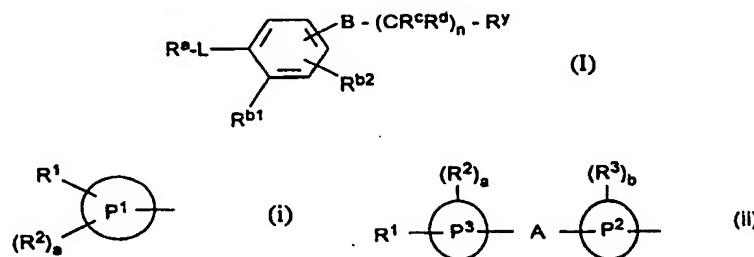
- 25
- removing any protecting groups,
 - converting a compound of formula (I) into another compound of formula (I), forming a pharmaceutically acceptable salt.

11. A compound according to any of claims 1 to 9 for use in therapy.
12. A pharmaceutical composition which comprises a compound according to any of claims 1 to 9 and a pharmaceutically acceptable carrier.

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07C 275/32, 233/29, 271/58, C07D 213/40, 401/12, 213/56, 401/14, A61K 31/17, 31/16, 31/395</p>	<p>A3</p>	<p>(11) International Publication Number: WO 98/50346</p> <p>(43) International Publication Date: 12 November 1998 (12.11.98)</p>						
<p>(21) International Application Number: PCT/EP98/02263</p> <p>(22) International Filing Date: 14 April 1998 (14.04.98)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>9707874.5</td> <td>18 April 1997 (18.04.97)</td> <td>GB</td> </tr> <tr> <td>9801632.2</td> <td>26 January 1998 (26.01.98)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): GASTER, Laramie, Mary [GB/GB]; (GB). WYMAN, Paul, Adrian [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).</p> <p>(74) Agent: WATERS, David, Martin; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p>		9707874.5	18 April 1997 (18.04.97)	GB	9801632.2	26 January 1998 (26.01.98)	GB	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 11 March 1999 (11.03.99)</p>
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(54) Title: ACETAMIDE AND UREA DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF CNS DISORDERS



(57) Abstract

Compounds of formula (I), processes for their preparation and their use as CNS agents are disclosed, in which R^a is a group of formula (i), in which P¹ is phenyl, bicyclic aryl, a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur; or R^a is a group of formula (ii); L is a group of formula -Y-C(=V)-DG-, in which Y is -NH-, NR⁵ where R⁵ is C₁₋₆alkyl, or Y is -CH₂- or -O-; V is oxygen or sulphur; D is nitrogen, carbon or a CH group, G is hydrogen or C₁₋₆alkyl providing that D is nitrogen or a CH group, or G together with R^{b1} forms a group W where W is (CR¹⁶R¹⁷), where t is 2, 3 or 4 and R¹⁶ and R¹⁷ are independently hydrogen or C₁₋₆alkyl or W is (CR¹⁶R¹⁷)_u-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, CR¹⁶=CR¹⁷, CR¹⁶=N, =CR¹⁶O, =CR¹⁶S or =CR¹⁶-NR¹⁷; B is CH₂, oxygen, S(O)_p where p is 0, 1 or 2, NR⁶ where R₆ is hydrogen or C₁₋₆alkyl or B is CR⁷=CR⁸ where R⁷ and R⁸ are independently hydrogen or C₁₋₆alkyl; R^c and R^d are independently hydrogen or C₁₋₆alkyl; R^e is a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or R^e is a group of formula -NR^fR^f in which R^e and R^f are independently hydrogen, C₁₋₆alkyl or aralkyl; R^{b1} and R^{b2} are independently hydrogen, halogen, hydroxy, C₁₋₆alkyl, trifluoromethyl, C₁₋₆alkoxy or aryl, or R^{b1} together with G forms a group W as defined above; and n is 0, 1, 2, 3 or 4.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02263

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C275/32 C07C233/29 C07C271/58 C07D213/40 C07D401/12
C07D213/56 C07D401/14 A61K31/17 A61K31/16 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	FR 1 176 918 A (RECHERCHES ET TECHNIQUES APPLIQUÉES ET AL) 17 April 1959 see page 2, column 1, lines 11-19; table 3, entries 10, 23	1,3,4, 6-8, 10-12
X	DE 22 26 009 A (E.R. SQUIBB & SONS INC) 25 January 1973 see examples 12, 20-24, 26, 27, 29, 32-34, 47-49, 51	1,3-8,10
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In: International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DE 40 36 782 A (BASF AG) 21 May 1992 see claims; example 1 ----	1,3,4, 6-8, 10-12
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P,X	EP 0 790 240 A (TANABE SEIYAKU CO LTD) 20 August 1997 see page 2, lines 47-54; page 15, lines 35-36; table 3, compound 22; table 5, compound 43 -----	1,4-8, 10-12

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